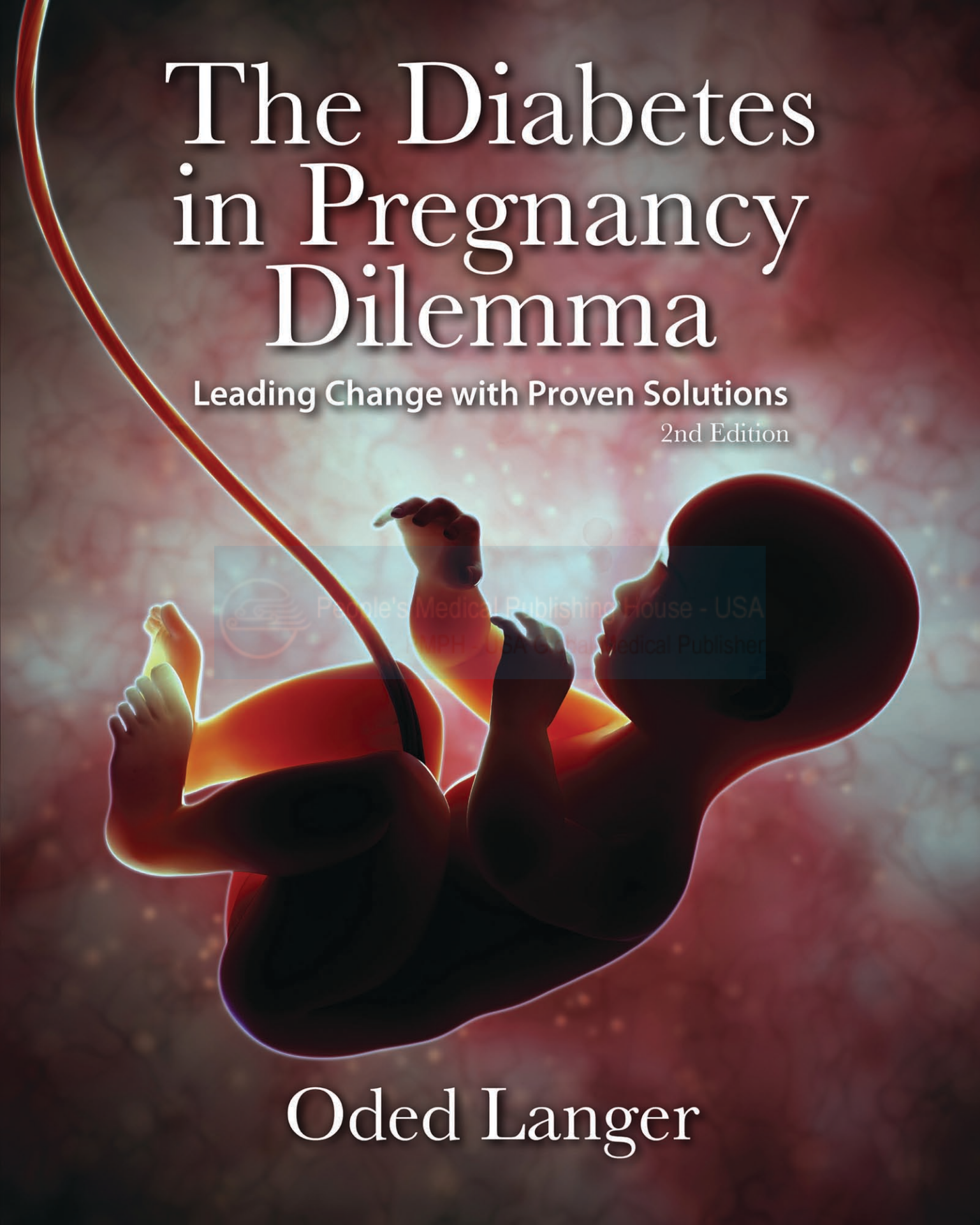
The Diabetes in Pregnancy Dilemma

Leading Change with Proven Solutions

2nd Edition



Oded Langer

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LEADING CHANGE WITH PROVEN SOLUTIONS

SECOND EDITION

Edited by

Oded Langer

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DEDICATION

This second edition of this textbook is dedicated to my family, with special recognition of my wife, Nieli. She has always believed that each partner must be allowed to grow; thanks for being there to inspire, encourage, and support me in pursuit of my goals. I am lucky to have been able to share them with you.

AND

To all my teachers and colleagues who have encouraged me to accept the challenges. I thank you. It is my firm belief that when you are through changing, learning, and accepting challenges, you are really through.

CONTENTS

PREFACE

The rationale for the publication of a second edition of the text was prompted by new advances in the field, the proliferation of more questions than answers in the areas of diagnosis and management, and the growth of outcomes research occurring against a backdrop of healthcare reform, managed care, cost containment, and quality improvement. Diabetes continues to be one of the most common medical complications in pregnancy, affecting women worldwide and even more prevalent in specific geographic regions and ethnic populations. Diabetes mellitus complicates pregnancy results, causing considerable maternal–fetal morbidity and mortality, adding substantial burdens on families and the healthcare system. In light of the fact that only 80% of women with gestational diabetes and 40–60% with preexisting diabetes achieve favorable glycemic control during pregnancy, our book, ***The Diabetes in Pregnancy Dilemma: Leading Change with Proven Solutions*** (Second Edition) specifically addresses the broad range of diagnostic and management issues presented by the diabetic mother and her fetus. The book incorporates state-of-the-art topics not usually addressed in books devoted to diabetes: history of the disease; the metabolic syndrome; obesity; threshold for treatment; oral hypoglycemic agents; type 2 diabetes; fetal growth restriction; patient empowerment, compliance, and pharmacotherapy; fetal safety; and ethical implications of treatment. The text provides the basis for practical skill development with a strong foundation in research synthesis founded on evidence-based medicine so that pregnancy has a successful outcome. The book, too, draws attention to the need for a multidisciplinary approach that will maximize whole-person care of the pregnant diabetic woman. As a result, the text not only provides a major source of up-to-date information, but also is a teaching tool for clinicians, investigators, diabetic educators, medical students, residents, and fellows; managed care teams (nurses, dietitians, and social workers); and medicine, family practice, endocrine, and obstetrics-gynecology (maternal–fetal specialists) faculty; and private practitioners in the management of diabetes in pregnancy.

To the extent that the book advances student, faculty, and practitioners' capacity to understand, conceptualize, and apply the information relevant to the needs of the pregnant diabetic and her fetus, I believe that we may continue to contribute to the quality of life and care of these persons. This textbook would not have been possible if not for the major contributions made by universal experts in the field. Many of the contributors are pioneers and leaders in the field of diabetes in pregnancy. They are my colleagues, collaborators, and friends. I thank them and salute their efforts.

Oded Langer, MD, PhD

INTRODUCTION

The Lay of the Land

Oded Langer, MD, PhD

Be who you are and say what you feel,
because those who mind don't matter and those
who matter don't mind.

—Dr. Seuss

History is interim reports issued periodically. The story of diabetes mellitus is a remarkable narrative covering 3500 years of medical history that closely parallels the documented human story. Studying this disease over time reveals a jarring fact: the incidence of diabetes has increased dramatically, from an uncommon complaint in ancient times to one that may potentially affect the lives of more than 300 million people by the year 2025.

THE RECOGNITION OF DIABETES IN ANTIQUITY

The earliest descriptions of the symptoms of diabetes are to be found in the recorded observations of ancient physicians. Ancient Egypt was the first civilization known to have an extensive study of medicine and to have left behind written records that describe the nature of ailments, their origins, practices, and procedures. The first reference to diabetes mellitus is attributed to the Ebers Papyrus. A German Egyptologist, Georg Ebers, acquired this papyrus in 1872, and the document relates to the ancient Egyptian practice of medicine and mentions remedies "to eliminate urine which is too plentiful" (polyuria). The passage, written about 1550 BCE, provides evidence that its sources were many centuries older.[1]

Egyptian medicine has influenced medical practices, including those of ancient Greece. While the writing of Hippocrates, the father of Greek medicine, describes excessive urinary flow with wasting of the body, Galen, his disciple, referred to the ailment as "diarrhea of the urine" and "the thirsty disease." Arataeus, Galen's contemporary, was the first to use the term "diabetes," meaning to pass through or to siphon, in connection with these symptoms. Arataeus described the afflicted patients as "never ceasing to make water and the discharge is an incessant sluice let off; the thirst is ungovernable."[1]

In another part of the ancient world, the Hindu physicians Charaka, Susruta, and Vaghbata described polyuria and glycosuria. The Hindu medical writings of the sixth century refer to diabetes as honey urine. They noted the attraction of flies and ants to the sweet urine of ailing patients.[2] In addition, the affliction was described as a "disease of the rich, brought about by gluttony or over-indulgence in flour and sugar."[3] Ancient Chinese and Japanese physicians likewise recognized the symptoms of diabetes. They bluntly described "the urine of diabetics was very large in amount and it was so sweet that it attracted dogs."[4]

KNOWLEDGE OF DIABETES IN THE MIDDLE AGES AND THE RENAISSANCE

The practice of medicine in the Middle Ages until approximately 1450 CE was fundamentally a restatement and acceptance of Greek practices. The famous Arabian physician Avicenna (980–1027) recorded further observations that maintained and extended the previous Greek knowledge of the disease. Avicenna observed that diabetic patients have an irregular appetite associated with thirst, mental exhaustion, and loss of sexual function. In fact, he described many of the symptoms and complications observed today, such as carbuncles and furuncles. In addition, he reported that diabetes probably affected the liver, causing its enlargement.[2]

Maimonides was a renowned medieval physician, rabbi, and philosopher. He claimed to have observed more than 20 cases while Galen, describing the condition as rare, documented having treated only two cases. Maimonides proposed that the sweet water of the Nile and the prevailing heat that spreads over the kidneys caused diabetes.[4] No major progress in understanding diabetes was made until the sixteenth century. Physicians began thinking of possible causes and exploring these ideas. Renaissance physicians, such as Paracelsus, challenged the medical doctrines of the time and attempted to reform medical thinking. They questioned conventional thinking with a renewed spirit of curiosity, objectivity, and experimentation. This period of reawakening in all disciplines accomplished two major breakthroughs in the approach and practice of medicine: it questioned authority and began to reject dogma by reverting back to the Socratic method of attempting to provide responses with evidence; and it laid the foundation for an accurate knowledge of human anatomy.

Thomas Willis, in 1674, was the first physician to rediscover and record the sweetness of the urine in diabetes referring to it as "the pissing evil." He proposed that diabetes was primarily a disease of the blood and not the kidneys. He made the best qualitative urinalysis studies possible at the time.[1] His work and Matthew Dobson's experiments 100 years later conclusively established the diagnosis of diabetes in the presence of sugar in the urine and blood. Cullen, a prominent British clinician and educator, added the descriptive adjective "mellitus" (1769) from the Latin word for honey. Cullen wrote to Dobson, "You have done something in putting it beyond all doubt by your experiments…." Thereafter, diabetes was no longer considered a rare ailment.[1,4]

The Experimental Period

Experimental work as early as 1682 by Brunner demonstrated that the pancreas was the diseased organ in diabetic individuals.[5] Experiments performed by Claude Bernard revealed that the liver releases a substance that affects blood sugar levels. In 1857, he

isolated a starch-like substance, which he called "glycogen," that was the precursor of glucose, "the internal secretion" of the liver. This observation established the role of the liver as a vital organ in diabetes.[6] Langerhans, in his doctoral thesis presented in 1769, described small islands within the pancreas now known as the islets of Langerhans, even though he acknowledged at the time that he did not know the function of these ductless cells.[7] Opie observed changes in the structure of the islet tissue of the pancreas of patients dying of diabetes. Minkowski's (1889) removal of the pancreas from a dog unexpectedly resulted in uncontrolled polyuria and the progression towards diabetes. The observational work of Opie and the experiments of Minkowski began to link islet cell disease and diabetes.[3,8] It was a major turning point in determining the endocrine function of the pancreas; it became clear that the substance secreted by the islet cells was inadequate in diabetic patients.

As with research in all diseases, many investigators concurrently work in different labs worldwide to find breakthroughs. Insulin was almost discovered in 1906 by Zuelzer in Berlin, in 1912 by Scott in Chicago, but was actually extracted by Paulesco in Romania in 1920. However, the world recognizes the definitive discovery and isolation of insulin to the Toronto group (1921–22), the collaborative work of Banting, Best, Collip, and Macleod.[9]

PREGNANCY AND DIABETES BEFORE THE DISCOVERY OF INSULIN

Diabetes was an affliction with a dismal prognosis. The dominant philosophy of the period before 1850 was that a successful pregnancy was virtually impossible when compromised by untreated diabetes. Pregnancy worsened the disease and shortened the lives of these women, many of whom died either during or shortly after the pregnancy. Blott wrote that "true diabetes is inconsistent with conception."[3] It was not until 1882 with Duncan's description of 22 pregnancies that the prevailing philosophy was questioned.[10] The trend, however, of high maternal and fetal mortality during or soon after pregnancy from uncontrolled diabetes persisted until the discovery of insulin. De Lee wrote that abortion and premature labor occurred in at least 33% of pregnancies of diabetic women. Perinatal mortality was close to 79%; maternal mortality about 30%, usually from diabetic ketoacidosis. In addition, diabetes was described as becoming progressively worse with each pregnancy.[11] It is necessary to note that unrelated to diabetes, at this point in time, maternal and neonatal mortality was high for many reasons. Poor interventional obstetric care with increased risk of puerperal sepsis in addition to social and economic deprivations further compromised pregnancies. The link between congenital malformations and maternal diabetes in pregnancy is of more recent concern because not only are the historical records on the frequency of congenital malformations incomplete, but also they were not specifically identified as a result of diabetic pregnancies. The interrelationship of preeclampsia to diabetes is also difficult to trace before organized antenatal care.[12]

THE ADVENT OF INSULIN FOR PREGNANCIES COMPROMISED BY DIABETES

Up until this time, the only effective treatment for diabetes has been dietary. Restriction of food was known to ameliorate the symptoms of the disease. John Rollo's work in 1797, as well as that of Allen in New York in 1919, documented a reduction in the symptoms of diabetes with a strict dietary regimen. Before the discovery of insulin, the work of Drs. Joslin of Boston and Laurence of London presaged the revolution in the treatment of diabetes and the potential for a positive pregnancy outcome for diabetic women. With the discovery and use of insulin, a new hope arose for diabetic women and their reproductive potential. With the introduction of insulin, maternal mortality fell dramatically but perinatal mortality decreased over time. However, the introduction of insulin did not ameliorate the problems of macrosomia and the associated traumatic injury to mother and fetus as well as continuing complications such as neonatal hypoglycemia, congenital malformations, preeclampsia, and infection.[13]

During the 1940s, insulin had made pregnancy relatively safe for the diabetic mother. However, patients with severe diabetes who in the pre-insulin era would never have been pregnant were now being treated. During this period, several attempts were made to ameliorate fetal death due to diabetes. It was observed that there was a significant stillbirth rate beyond 36 weeks of gestation. As a result, diabetic patients were routinely delivered at or before 36 weeks by cesarean section or by induction of labor if fetal death had not already occurred or if maternal complications indicated an early delivery. Today, when cesarean section is being performed for more and more indications, some researchers during the 1940s cautioned against adding another indication. Shir wrote, "Cesarean section is still a dangerous operation and diabetes does not render it less so."[14]

During this time, several clinics were organized in the United States and Europe for the care of pregnant women with diabetes using an interdisciplinary approach featuring the cooperation of diabetologists, obstetricians, and pediatricians. Pedersen[15] in Denmark found that fetal mortality rate was significantly lower in patients who were followed throughout pregnancy in comparison to those who were first diagnosed with the disease at or about the time of delivery. There was an emerging philosophy that closer surveillance and more frequent patient visits improved fetal outcome. Thus, long-term management, frequent hospitalizations, and early delivery became the norm. At the Joslin Clinic in Boston under the leadership of Priscilla White,[16] new clinical recommendations for the care of pregnant diabetic women consisted of strict glycemic control, long-term hospitalization, and sound obstetrical management.

During the 1950s, risk factors for the development of abnormal carbohydrate metabolism in pregnancy were defined. In addition, screening programs were proposed, and soon thereafter normal values for the interpretation of the glucose tolerance test (OGTT) were suggested.[17–18]

Gestational diabetes as a clinical entity

Gestational diabetes (GDM), defined as "carbohydrate intolerance of varying severity with onset or first recognition during pregnancy," is a fairly recent addition to our knowledge about diabetes in pregnancy. In the first recorded case, Bennewitz considered diabetes a symptom of the pregnancy, and since the symptoms and the glycosuria disappeared after two successive pregnancies, he had some evidence to support his views.[19] Other studies conducted in the United States and Scotland during the

1940s reported that lesser degrees of maternal hyperglycemia were also a risk to pregnancy outcome.[20–22] O'Sullivan first used the term gestational diabetes in 1961. In the United States, the emphasis was on establishing criteria for the 100-g oral glucose tolerance test in pregnancy as an index of the subsequent risk of the mother to develop diabetes; the well-known O'Sullivan criteria were derived from this foundation.[23] At about the same time, Mestman reported increased perinatal mortality associated with abnormal oral glucose tolerance in the obstetric population of Los Angeles County Hospital. Most of the women were either Latino (60%) or African-American; few Caucasians were represented in this population.[24] Gestational diabetes as a clinical entity was slow to win converts, partly because of the relatively short phase of hyperglycemia during the latter part of pregnancy and its disappearance after the delivery. It has become increasingly accepted as a disease not only for the immediate outcome of pregnancy but also for the long-term effects on child and mother (maternal development in later life of type 2 diabetes).[19]

MODERN ERA IN THE MANAGEMENT OF DIABETES IN PREGNANCY

Strong pressures were exerted by the medical community to develop methods to increase the rate of insulin release from its injection site so that control of blood sugar concentrations could be improved. Over the years, pharmaceutical laboratories have developed increasingly reliable and stable insulin preparations. Monomeric insulin preparations are now established in the repertoire of clinical therapies. Human insulin became widely available in the 1980s. This led to the availability of mutant insulin (insulin analogues) that was designed primarily to have improved pharmacokinetic features for subcutaneous administration.

The modern era in the management of diabetes in pregnancy began in the 1960s with the introduction of reliable chemical and/or physical measures to assess gestational age, fetal well-being, and placental function: ultrasonography made early assessment of gestational age and accurate fetal growth determination possible[25]; the biophysical profile became routine in the management of high-risk pregnancies[26]; antepartum fetal heart rate testing was introduced; and Gluck et al. proposed the determination of the lecithyin-to-sphingomyelin ratio in the amniotic fluid as a test for fetal lung maturity.[27] With proper use and interpretation of these tests, two of the four causes of fetal loss were reduced: sudden intrauterine death and neonatal death caused by hyaline membrane disease. In addition, physicians were able to avoid unnecessary early delivery. Other advances included fetal blood-sampling techniques during labor, glucose monitoring, insulin pumps, and neonatal intensive care units.

In 1977, Karlsson and Kjellmer[28] reported that there was a linear relationship between glycemic control and perinatal mortality. It was the advent of self-monitoring blood glucose that made possible strict blood sugar control from early pregnancy on and a resulting decline in adverse neonatal events. The results of this technology and other corroborating evidence led to intensified glucose management to as close to nondiabetic levels as possible; perinatal mortality began to decrease.[29–30]

Except for coronary artery disease, pregnancy has not been shown to be contraindicated in diabetic women with vascular complications. Perinatal outcome does not appear to be significantly different from other insulin-dependent diabetes when metabolic control is stringently maintained.[31] Studies have suggested that congenital malformations are caused by derangement in metabolism during organogenesis.[32] During the 1980s a major effort was mounted to control blood sugar before conception. The findings from Fuhrman's study demonstrated that normalization of metabolism with tight glycemic control during preconception and the organogenesis period can reduce the incidence of congenital malformations.[33] However, women become pregnant without having achieved established levels of glycemic control despite preconception counseling.

Scientific evidence demonstrates that self-management education with self-monitoring blood glucose is the cornerstone of care for all persons with diabetes. In pregnancy, human insulin is recommended since the use of insulin analogues has not been adequately tested. Data on insulin lispro and insulin aspart are limited. Studies have demonstrated an improvement in glycemic control, an increased patient satisfaction, and a decrease in hypoglycemic episodes; but there is scant data on maternal and neonatal outcomes.

Intensified therapy in the management of GDM and pregestational diabetes is an approach to achieving established levels of glycemic control. It involves memory-based, self-monitoring blood glucose (SMBG), multiple injections of insulin or its equivalent, control of diet, and an interdisciplinary practitioner effort. Regardless of the treatment modality used, insulin or oral anti-diabetic drugs, the purpose is to achieve the established level of glycemic control that diminishes the rate of hypoglycemia and ketosis and maximizes perinatal outcome. As suggested by Freinkel,[34] "normalizing maternal–fetal metabolism throughout every day of pregnancy would result in healthy infants, with a potential of achieving normal intellectual and growth development."

WHAT HAVE BEEN, AND CONTINUE TO BE, THE *DILEMMAS* ASSOCIATED WITH DIABETES IN PREGNANCY?

A *dilemma* refers to a difficult or persistent problem. Major life dilemmas are associated with ill health. "When health is absent, wisdom cannot reveal itself, art cannot become manifest, strength cannot be exerted, wealth is useless, and reason is powerless." (Herophilus, an ancient Greek physician).

Pregnancy is a special time in a woman's life when she is coping with the anxiety of the pregnancy, delivery, and welfare of the fetus. This waiting period becomes even more anxiety-producing if the pregnancy is complicated with diabetes. Diabetes constitutes one of the most common and significant complications of medicine in general and pregnancy in particular. Every pregnant woman needs and should expect high-quality, evidence-based medical care. We, as women's health physicians, should be satisfied with providing nothing less.

Measuring the success of treatment is based on the evaluation of the outcome in a given complication. The Saint Vincent's Declaration (October, 1989) targeted the achievement of pregnancy outcomes in diabetic women to approximate those of nondiabetic women within the forthcoming 5-year period. This was not only the summary statement of the meeting organized

by WHO and the IDF, but also a challenge to all clinicians and researchers interested in diabetes in pregnancy. A difference, in order to be a difference, must make a difference. Today, almost 25 years later, morbidity and mortality data in both GDM and pre-existing diabetes remain relatively unchanged.[35–36] The debate of the past few decades over whether gestational diabetes is a clinical entity[37–39] has been resolved, demonstrating that treatment can improve pregnancy outcome. Yet, in both medical forums and academic research, the diabetes in pregnancy community of clinicians and researchers has been too engrossed in fine-tuning diagnostic criteria and not more vigorously invested in pregnancy outcome. If we want to change our minds, we have to change our exposure. Changing our fixed ideas or positions doesn't happen quickly—it is often a slow and tedious process. Integration and relationship-building by people (clinicians and researchers) talking to the peers they trust who represent the change in question is the route to sounder medical practice with fewer turf wars. The focus for the next decade is to respond to the outcome dilemma by seeking the means to uphold the Saint Vincent's Declaration. Worldwide collaboration and dissemination of information is still the cornerstone for stimulating ideas and encouraging creative, evidence-driven research. This focus may help make the content of the St. Vincent's Declaration a reality.

"Measurement is the first step that leads to control and improvement. If you can't measure something, you can't understand it. If you can't understand it, you can't control it. If you can't control it, you can't improve it" (H. James Harrington). What to test and how to test in diabetes management remains another unresolved dilemma, especially with the introduction of new technology: that is, self-monitoring blood glucose, continuous blood glucose insulin pumps, and continuous blood glucose monitoring. Another dilemma in need of resolution is an efficient and efficacious means to analyze the data generated by these technologies in order to enhance diabetes management. Still another significant dilemma involves the as yet not well defined threshold that needs to be targeted to initiate and maintain glucose control.

To date, there are numerous logarithmic formulae for estimating fetal weight, but there is a lack of uniformity and accuracy in measurement. Virtually all EFW (estimated fetal weight) formulae systematically overestimate birth weight. The imprecision of the formulae to account for fat deposits in fetuses and difficulties in measuring the abdominal circumference (AC) of fetuses of diabetic mothers may provide another explanation for the inaccuracies in EFW. However, most formulae are better at predicting macrosomia than are predictions based on gestational age alone. In infants of women with poorly controlled diabetes, there is characteristic enlargement of the majority of the organs but not of the brain. Increased weight of insulin-sensitive tissues including liver, pancreas, heart, lungs, and adrenals has been demonstrated in the infants of diabetic mothers (e.g., an increase in liver size of 179%). On the basis of this finding, it was suggested that morphometry be used to measure fetal liver length.

It was found that the increase in liver length was evident as early as the 18th week of gestation and became more marked with increased duration of pregnancy. Furthermore, individual liver length measures did not always remain constant when they were followed serially throughout pregnancy. This approach may provide an early fetal marker in addition to maternal markers (level of glycemia) for initiation of pharmacological therapy. Neonatal fat contributes approximately 12–14% of total birth weight; it accounts for about 50% of the variance. However, the amount of fetal fat in the subcutaneous locations used in anthropometric models may account for 40–80% of total fetal fat.[40]

The evaluation of the fetus of a diabetic mother should include in the first trimester a transvaginal ultrasound examination to rule out gross congenital abnormalities and CRL (crown rump length) measurements for dating. A complementary abdominal ultrasound examination for congenital malformations needs to be performed at approximately 20–23 weeks' gestation. AC (abdominal circumference), fetal weight estimation, body composition, and cardiac evaluation (echocardiography) will enhance identification of the constitutionally large or small infants. During the third trimester, serial sonographic measurements need to be performed in order to assist in the selection of the treatment modality and the detection of deviant fetal growth.[41]

For pre-existing diabetes, preconception care is a major dilemma if we seek to adequately address the problem of congenital malformation. To date, the majority of women attend the first prenatal visit after organogenesis. For GDM (gestational diabetes mellitus), the window of opportunity for affecting outcome is narrow, that is, 8 to 12 weeks. Criteria for the assignment of treatment modality are lacking; that is, should treatment be based on diet alone, diet and exercise, insulin, or oral hypoglycemic agents? Furthermore, there is no benchmark for altering therapy when the desired glycemic results have not been achieved. We clinicians and researchers agree that early diagnosis, adequate treatment, and close follow-up are essential in order to minimize and often eliminate many of the diabetes-related complications. In our zeal to diagnosis and treat, however, we have not established universal criteria that enable a fluid, less controversial, less error-prone route towards enhanced perinatal and maternal outcome.

In light of extended life expectancy and adequate diabetic management for both the pregnant and nonpregnant patient, we need to address the diabetes epidemic worldwide when the number of known and undiagnosed individuals (approximately 9% for type 2 in the United States alone) is reaching staggering proportions. The double medical offensive of diabetes and obesity, that is, "diabesity," with their short- and long-term complications contributes an additional dilemma of how to maximize maternal care before pregnancy. We, as women's healthcare practitioners, are responsible for women throughout the life cycle and not solely during pregnancy.

The goal of the second edition of this textbook is to provide a forum to mitigate the dilemmas caused by diabetes in pregnancy by offering evidence-based responses by world-renowned clinicians and researchers often working and writing together in pursuit of this goal. The above-described dilemmas in no way seek to minimize the significance of basic science research in pathophysiology, immunology, and metabolic pathways associated with diabetes in pregnancy. Perhaps mapping of the human genome, which marks a new era in scientific research in the twentyfirst century, will provide the next chapter to be written in the history of diabetes.

I, and my distinguished group of expert contributors, have sought to provide a comprehensive approach to a very important topic. The book will be of interest and of help not only to obstetricians and gynecologists, but also to endocrinologists, internists,

and primary care physicians. Every health professional who cares for women of reproductive age must be concerned with issues of gestational and pregestational diabetes. These include fetal macrosomia, congenital malformations, spontaneous abortions, and also complications arising as a result of obesity, hypoglycemia, hypertension, including retinopathy and nephropathy. A comprehensive understanding and firm foundation in the knowledge of the potential disease complications will positively alter the success rate for both mother and infant.

Women with diabetes want to have children and want to deliver them healthy while addressing the complications of their own disease. To the extent that this text advances student, faculty, and practitioners' capacity to understand, conceptualize, and apply the information relevant to the needs of the pregnant diabetic and her fetus, I believe that we may contribute to the quality of life and care of these persons. We the authors hope that the information and the recommendations offered in this text will advance this mission.

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SECTION I The Scientific Rationale for Global Issues Affecting Diabetes in Pregnancy

The Professional Responsibility Model of Obstetric Ethics

1

Clinical Application to the Management of Diabetes in Pregnancy

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The greatest mistake in the treatment of diseases is that there are physicians for the body and physicians for the soul, although the two cannot be separated…

—Plato

Key Points

- The professional responsibility model of obstetric ethics is an essential dimension of the obstetrical management of diabetes in pregnancy.
- Beneficence is the ethical principle that obligates physicians to seek the greater balance of clinical good over clinical harm in patient care.
- Respect for autonomy is the ethical principle that obligates the physician to empower pregnant patients in the informed consent process.
- The fetus is a patient when it is presented to the physician, and clinical interventions exist that are reliably expected to protect and promote the health-related interests of the fetus.
- When the fetus is not a patient, nondirective counseling regarding continuation of pregnancy is appropriate.
- The physician's position on mode of delivery should be based on a careful consideration of beneficence-based obligations to the pregnant woman and fetal patient, and autonomy-based obligations to the pregnant woman.
- The patient's preferences for mode of delivery should be considered but are not decisive in beneficence-based clinical judgment in the professional responsibility model of obstetric ethics.
- In areas of scientific disagreement, when beneficence-based clinical judgment is uncertain, the patient's preferences have a more decisive role to play in determining mode of delivery.
- Professionally responsible clinical judgment about the management of pregnancies complicated by diabetes should be based on beneficence-based and autonomy-based obligations to the pregnant woman and beneficence-based obligations to the fetal patient.

INTRODUCTION

Physicians caring for a pregnant woman with diabetes will face and need to responsibly manage the ethical issues that arise when the physician's judgments about what is in her and/or the fetus' clinical interest differ from the woman's judgment about these interests. One way to manage such differences would be to claim that the physician's judgment should control decision making. This strategy has been discredited as it leans toward practitioner paternalism. Paternalism occurs when the physician's clinical judgments fail to take into account the patient's values and beliefs and interfere with her preferences regarding her own health and medical care. To avoid paternalism, the physician could opt for the alternative, that is, the patient's judgment being the controlling factor in decision making. This approach, however, reduces the physician's role to that of mere technician; worse, this approach may require the physician to act in ways that contradict reasonable medical judgment.[1]

In this chapter, we avoid these two extremes by applying the professional responsibility model of obstetric ethics to the challenges of decision making by the obstetrician and the pregnant woman with diabetes about what is in her best interests.[2] We begin by explaining the professional responsibility model of

obstetric ethics. We then identify the implications of the professional responsibility model for the role of cesarean delivery in the care of pregnant women with diabetes. This chapter emphasizes a preventive ethics approach that appreciates the potential for ethical conflict and adopts ethically justified strategies to prevent those conflicts from occuring.[1,3] Preventive ethics helps to build and sustain a strong physician–patient relationship.

THE PROFESSIONAL RESPONSIBILITY OF OBSTETRIC ETHICS

The professional responsibility model of obstetric ethics appeals to the ethical concept of medicine as a profession. Many obstetricians believe that medical professionalism has roots in the Hippocratic Oath and other ethical texts in the Hippocratic Corpus. This belief does not withstand close scrutiny, because the Hippocratic Oath can reasonably be read as a guild oath, the primary purpose of which was to secure the fealty of young men who were not the sons of physicians of the Coan School and other groups of physicians who subscribed to the tenets of the Oath. The first section of the Oath stipulates the obligations of these young men to their masters in the guild. The prescriptions and proscriptions of the Oath are not explained but can be read as self-interested, for example, avoiding high mortality rates and the ruined reputation that they bring in their wake to physicians whose patients die in high numbers from pessaries (major sources of infection for women into whose vaginas the pessaries would be placed to induce uterine contractions and abortion of a fetus) or from surgery, even from "the stone," that is, bladder stones that can be discovered upon palpation. The Oath calls for the protection of technè, rather than patients, as its primary focus. Technè is wrongly translated as the "art" of medicine, in contrast to the science of medicine, because technè names the "science" of ancient Greek medicine. We use the scare quotes to indicate that technè is not science but a fixed, unchanging, and unchangeable body of knowledge about the four humors and their imbalances and the clinical skills of diagnosing the course and severity of diseases and injuries and intervening very modestly to alter that course. From the perspective of modern, genomic scientific medicine, to make the Oath and accompanying texts the basis of professionalism in medicine is very odd, indeed.

Suppose, for the sake of argument, that the Hippocratic Corpus does indeed present a concept of medicine as a profession rather than an unchanging, self-interested guild that comes down to us intact from ancient Greece in what is usually invoked as the "Hippocratic Tradition." Vivian Nutton has shown that there was no Hippocratic tradition.[4] The Oath fell out of favor in the early centuries of the Common Era. In medieval and Renaissance universities, graduates in medicine took an oath of loyalty to the faculty. Nutton shows that the mid-twentieth century witnessed a conservative reaching back to the revered founder of Western medicine to valorize a set of values that did not originate in ancient Greece. Galvão-Sobrinho has shown that this is a common use of the historical figure of Hippocrates to give value to views that the Hippocratic physicians would not recognize and are even incompatible with the content of the Hippocratic texts.[5]

The ethical concept of medicine as a profession originates much more recently, during the Scottish and English Enlightenments.[6,7] Two physician–ethicists, John Gregory (1724–1773) of Aberdeen and Edinburgh in Scotland and Thomas Percival (1740–1804) of Warrington and Manchester in England conceived the ethical concept of medicine as a profession in response to the guild mentality that had come to dominate Western medicine as a legacy of the Hippocratic Oath. The individual and group self-interest was epitomized in the *Statuta Moralia* of the Royal College of Physicians in London. These "moral statutes" were designed to promote the self-interest of physicians in such matters as cultivating good reputations by never criticizing each other in public.[6]

In eighteenth-century British medicine, there was no accepted science of medicine and, therefore, no accepted educational pathway into medical or surgical practice. Instead, there were almost as many concepts of health and disease and treatments as there were physicians. Physicians competed fiercely for the small private practice market in the homes of the well-to-do, emphasizing self-interest and survival in a fiercely competitive market. Gregory and Percival also wrote their medical ethics in response to the crisis of trust of the sick. Dorothy and Roy Porter have convincingly documented that, at that time, sick persons did not trust physicians, surgeons, and apothecaries (forerunners of modern pharmacists) intellectually to know what they were doing or morally to be concerned about the well-being of the sick; they were concerned, however, with lining their pockets with the money of the sick.[8]

Gregory and Percival reformed medicine into the profession that it has become over the past two centuries. They did so by turning to the best scientific method of their day, Baconian, experience-based medicine (a forerunner of what is now known as evidence-based medicine or the deliberative practice of medicine). They embraced the best moral science of their day, Gregory to David Hume's sympathy-based moral science and philosophy (1711–1776) and Percival to Richard Price's (1723–1791) intuition-based moral science and philosophy.[7]

Drawing on these intellectual resources, Gregory and Percival put forward the ethical concept of medicine as a profession with three components. First, physicians should commit to becoming and remaining scientifically and clinically competent. Second, physicians should use their scientific and clinical competence primarily to protect and promote the health-related interests of patients, keeping individual self-interest systematically secondary. Third, physicians should commit to sustaining medicine as a public trust (the phrase is Percival's) that exists primarily for the benefit of patients and society, keeping group or guild self-interest systematically secondary.[7] The result of Gregory and Percival's pioneering medical ethics was to transform physicians from incompetent, self-interested practitioners into professional physicians. The sick were transformed into patients. Thus was introduced into the history of medical ethics the physician–patient relationship that is professional and not primarily contractual in nature.

The professional virtue of integrity is based on the ethical concept of medicine as a profession. Professional integrity comprises two commitments. The first is to intellectual excellence that is achieved by making the first commitment in the ethical concept of medicine as a profession. The second is to moral excellence that is achieved by making the second and third commitments in the ethical concept of medicine as a profession. Professional integrity

sometimes requires health care professionals to protect patients from themselves. In this respect, the ethical concept of medicine is justifiably paternalistic in nature: It rests on the assumption that scientific and clinical competence creates expertise about health care that the typical patient does not possess.

The ethical concept of being a patient is a function of the ethical concept of medicine as a profession. A human being becomes a patient when he/she presents to a physician or other health care professional for clinical management. It is expected that the physician's deliberative (evidence-based, rigorous, transparent, and accountable) clinical judgment will result in a net clinical benefit for that person. The ethical concept of being a patient is beneficence-based.[1,2]

The professional responsibility model of obstetric ethics applies the ethical concept of medicine as a profession to obstetric practice.[2] During the intrapartum period, the obstetrician has two patients, the pregnant patient and the fetal patient, when the pregnant woman presents for care. The obstetrician, therefore, has beneficence-based obligations to both the pregnant and the fetal patients to protect and promote their health-related interests. The obstetrician also has autonomy-based obligations to the pregnant woman. These obligations focus on empowering the pregnant woman with information that she needs to make decisions with her obstetric health care professional about the management of her pregnancy. The obstetrician must in all cases take into account and balance beneficence-based and autonomy-based obligations to the pregnant patient and beneficence-based obligations to the fetal patient. This ethically complex relationship means that the fetal patient is not a separate patient, that is, beneficence-based obligations to the fetal patient are a part of, but not the entirety of, the ethical relationship between the obstetric health care professional and the pregnant patient and fetal patient.[1,2]

The professional responsibility model of obstetric ethics stands in sharp contrast to what we have elsewhere described as the maternal-rights-based reductionist model of obstetric ethics.[2] In this model, the pregnant woman's autonomy is the controlling ethical consideration throughout pregnancy. She has an absolute right to bodily integrity unconstrained by any ethical obligations to the fetus. The fetus is not a patient in this account but is ethically separate from the pregnant woman. This model has important implications for the relationship between the pregnant woman and the obstetrician. The relationship is purely contractual because the sole basis of the relationship is the exercise of the pregnant woman's autonomy. In the professional responsibility model, the pregnant woman's right to bodily integrity is not absolute; it is an ethically significant component of autonomy-based obligations to the pregnant woman but not the sole controlling ethical consideration, as it is in the rights-based reductionist model of obstetric ethics.

The maternal-rights-based reductionist model has a radical implication that its advocates ignore. In such a model of health care, there are no patients. There are only sick individuals (*aegrotrus* in the Latin texts that precede Gregory and Percival in the history of Western medical ethics) or clients who contract with providers. There are no health care professionals, because rights-based-reductionist models embrace an absolute right to bodily integrity of the client, which eliminates professional integrity as an ethically justified constraint on the client's autonomy because it prevents the physician from intervening in a professional manner.

In the professional responsibility model of obstetric ethics, when the fetus is a patient, directive counseling for fetal benefit is ethically justified. In clinical practice, directive counseling for fetal benefit involves one or more of the following: recommending against termination of pregnancy; recommending against nonaggressive management; or recommending aggressive management. Aggressive obstetric management includes interventions such as fetal surveillance, tocolysis, cesarean delivery, or delivery in a tertiary-care center when indicated. Nonaggressive obstetric management excludes such interventions. Directive counseling for fetal benefit, however, must always take into account the presence and severity of fetal anomalies, extreme prematurity, and obligations to the pregnant woman.[1]

It is important to appreciate in obstetric clinical judgment and practice that the strength of directive counseling for fetal benefit varies according to the presence and severity of anomalies. As a rule, the more severe the fetal anomaly the less directive counseling should be for fetal benefit.[1,9–11] In particular, when there is "(1) a very high probability of a correct diagnosis, and (2) either (a) very high probability of death as an outcome of the anomaly diagnosed or (b) very high probability of severe irreversible deficit of cognitive developmental capacity as a result of the anomaly diagnosed," counseling should be nondirective in recommending between aggressive and nonaggressive management options.[9–11] By contrast, when lethal anomalies can be diagnosed with certainty, there are no beneficence-based obligations to provide aggressive management.[9–11] Such fetuses are appropriately regarded as dying fetuses, and the counseling should be nondirective in recommending between nonaggressive management and termination of pregnancy, but directive in recommending against aggressive management for the sake of maternal benefit.[12]

The strength of directive counseling for fetal benefit in cases of extreme prematurity of viable fetuses does not vary. In particular, this is the case for what we term just-viable fetuses,[1] those with a gestational age of 24–26 weeks, for which there are significant rates of survival but high rates of mortality and morbidity.[13] These rates of morbidity and mortality can be increased by nonaggressive obstetric management, while aggressive obstetric management may favorably influence outcome. Thus, it would appear that there are substantial beneficence-based obligations to just-viable fetuses to provide aggressive obstetric management. This is all the more the case in pregnancies beyond 24 weeks gestational age.[13] Therefore, directive counseling for fetal benefit is justified in all cases of extreme prematurity of viable fetuses, considered by itself. Of course, such directive counseling is ethically justified only when it is based on documented efficacy of aggressive obstetric management for each fetal indication.

Directive counseling for fetal benefit must always occur in the context of balancing beneficence-based obligations to the fetus against beneficence-based and autonomy-based obligations to the pregnant woman[1,14] (Table 1-1). Any such balancing must recognize that a pregnant woman is obligated only to take reasonable risks of medical interventions that are reliably expected to benefit the viable fetus or child later. The unique feature of obstetric ethics is that whether, in a particular case, the viable fetus ought to be regarded as presented to the physician is, in part, a function of the pregnant woman's autonomy.

TABLE 1-1 Ethical Obligations of the Physician in Obstetric Care

Interests of Pregnant Woman		Interests of Fetal Patient	
Maternal Autonomy-Based Obligations of Physician	Maternal Beneficence-Based Obligations of Physician	Fetal Beneficence-Based Obligations of Pregnant Woman	Fetal Beneficence-Based Obligations of Physician

Obviously, any strategy for directive counseling for fetal benefit that takes into account the obligations to the pregnant woman must be open to the possibility of conflict between the physician's recommendation and a pregnant woman's autonomous decision to the contrary. Such conflict is best managed preventively through informed consent as an ongoing dialogue throughout the pregnancy, augmented as necessary by negotiation and respectful persuasion.[1,3]

Counseling the pregnant woman regarding the management of her pregnancy when the fetus is previable should be nondirective in terms of continuing the pregnancy or having an abortion if she refuses to confer the status of being a patient on her fetus. If she does confer such status in a settled way, at that point beneficence-based obligations to her fetus come into existence and directive counseling for fetal benefit becomes appropriate for these fetuses. Just as for viable fetuses, such counseling must always also take into account the presence and severity of fetal anomalies, extreme prematurity, and obligations owed to the pregnant woman.

For pregnancies in which the woman is uncertain about whether to confer such status, the authors propose that the fetus be *provisionally* regarded as a patient.[1] This justifies directive counseling that the woman not engage in behavior that can harm a fetus in significant and irreversible ways, for example, poorly controlled hyperglycemia, until the woman settles on whether to confer the status of being a patient on the fetus. This also justifies directive counseling about diagnostic surveillance, for example, ultrasound examination to detect anomalies. When anomalies are detected, counseling about the disposition of the woman's pregnancy should be nondirective, as explained earlier.

Nondirective counseling is appropriate in cases of what we term near-viable fetuses,[1] that is, those who are 22–23 weeks gestational age for which there are anecdotal reports of survival.[13] In the authors' view, aggressive obstetric and neonatal management should be regarded as clinical investigation, that is, a form of medical experimentation—not standard of care. There is no obligation on the part of a pregnant woman to confer the status of being a patient on a near-viable fetus, because the efficacy of aggressive obstetric and neonatal management has yet to be proven.[13]

WHEN TO OFFER, RECOMMEND, AND PERFORM CESAREAN DELIVERY

When to offer, recommend, and perform cesarean delivery presents clinical ethical challenges to the obstetrician in the management of a pregnancy complicated by diabetes. The professional responsibility model of obstetric ethics provides reliable, clinically applicable guidance for the management of these challenges. This approach is designed to prevent conflict between the obstetrician and the pregnant woman about intrapartum management.

Our approach begins by asking, "Is cesarean delivery substantively supported and vaginal delivery not supported in beneficence-based clinical judgment?"[15] Such cases occur with diabetic pregnancies, based on the clinical factors such as estimation of fetal weight and the maternal pelvis, degree of control of diabetes in the pregnancy, and previous obstetric history. These clinical factors are discussed in detail elsewhere in this volume. When the best available evidence or otherwise reliable clinical judgment supports the view that the fetus's interests are best protected by cesarean delivery, and there are no maternal contraindications, the professional responsibility model supports offering and recommending cesarean delivery.

In some clinical circumstances, there is scientific controversy as to whether cesarean delivery is the better alternative. Competing well-founded beneficence-based clinical judgments regarding how to balance the fetal benefit of preventing harm of cesarean delivery generate these controversies, which are discussed elsewhere in this volume. Whenever there is legitimate scientific disagreement about the benefits and risks of cesarean versus vaginal delivery, the professional responsibility model calls for both options to be offered to the pregnant woman and discussed with her so that she can meaningfully exercise her autonomy in the informed consent process. This approach empowers the woman to emphasize her own perspective in balancing maternal and fetal benefits and risks. It is appropriate for the obstetrician to assist the woman's decision making about both options in the form of a recommendation.

In clinical circumstances, when cesarean delivery is substantively supported in beneficence-based clinical judgment but vaginal delivery is more substantively supported, vaginal delivery is the better alternative, but not the only one, for example, a pregnant woman with diabetes whose sugars have been well controlled during pregnancy and there is no macrosomia. Although cesarean delivery is supported in beneficence-based clinical judgment, trial of labor is more substantively supported. Therefore, the professional responsibility model supports offering and recommending trial of labor.

SUMMARY

The professional responsibility model of obstetric ethics is an essential dimension of obstetric practice, especially the care of pregnant women with diabetes. In this chapter, we have described the professional responsibility model of obstetric ethics. We have deployed this model to address when to offer and recommend cesarean delivery. We believe that the clinical application of the professional responsibility model of obstetric ethics will strengthen the obstetrician–patient relationship and, therefore, enhance the quality of care for pregnant women with diabetes.

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Evidence-Based Medical Practice

Its Use and *Misuse*

2

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Where is the wisdom we have lost in knowledge and where is the knowledge we have lost in information?

—T.S. Eliot

Key Points

- Evidence-based medical practice (EBMP) *may* provide:
  1. Encouragement for rigorous testing of practice-related claims regarding effectiveness
  2. Means for disseminating practice-related research findings
  3. Enhanced opportunities for doing more good than harm
- EBMP is a bridge between external clinical evidence and individual clinical practice.
- EBMP has many partners and entangling alliances.

INTRODUCTION

The goal of education and research in all disciplines is to develop critical thinking skills as a method for improving clinical decision making. Critical thinkers explore their own attitudes and values, investigate and analyze competing alternatives, and are motivated to articulate their point of view. The emphasis on critical thinking is nothing new and can be traced back to ancient times where Socrates believed in education by interrogating rather than by propounding. Socrates challenged his students to think about their knowledge, beliefs, and behaviors. It is widely known that Socrates would press his students until they could provide evidence to support their arguments and would dismiss those beliefs and decisions that could not be supported with proof.

Evidence-based medical practice (EBMP) originated in health care in the mid-twentieth century as an alternative to authority-based practice (i.e., basing decisions on so-called experts' opinions). EBMP offers practitioners and administrators a foundation that is compatible with professional codes of ethics (i.e., for informed consent) and educational accreditation policies and standards. Although most people engaged in meaningful careers in health care will, in all probability, never conduct empirical research, they will be reading research articles in their professional journals that describe issues relevant to their practices. EBMP is designed to enhance practitioners' ability to be good consumers of research. If practitioners are not familiar with up-to-date evidentiary practices and policies, they are not providing their patients with the best medical alternatives. Moreover, they cannot honor informed consent obligations to provide best possible care. To access, analyze, and apply research findings in health care, practitioners will need to understand why, by whom, and how research studies are conducted.

In light of the above, it is amazing that it took until the 1990s when a group of clinicians and epidemiologists at McMaster University in Ontario, Canada, officially coined the term "evidence-based medicine." We cannot help but smile and believe that Socrates would look favorably on the evolution of EBMP while reminding us that we need additional evidence and the dissemination of critical thinking skills to support its use.

EBMP is a medical movement based on the application of the scientific method to medical practice, including long-established existing medical traditions not yet subjected to adequate scientific scrutiny. It originated because of gaps among evidentiary, ethical, and application concerns. From the beginning, the concept faced mixed reviews: excitement from researchers and resentment from health care practitioners who deemed it impractical in busy medical offices. Our attempts since ancient times have been to increase medical knowledge and enhance the level of medical care. The 21st century has witnessed the confluence of an accumulation of knowledge, in addition to the tools to access and deliver the fruits of this knowledge to all interested health care providers.

THE BRIDGE BETWEEN EXTERNAL CLINICAL EVIDENCE AND INDIVIDUAL CLINICAL PRACTICE

Advantages of Randomized Clinical Trials

It took until the middle of the 20th century before medical science was to help facilitate the evolution of the *randomized clinical trial* (RCT) that generates some of the information that becomes evidence. In medicine, since the randomized controlled trial, when conducted under the appropriate conditions, is so much more likely to inform us and so much less likely to mislead us, it has become the gold standard for judging whether a treatment does more good than harm.[1] As the least biased form of medical evidence, the RCT offers many advantages. It provides the strongest evidence of causality and represents the best methodology to test the effectiveness of an intervention, that is, the extent to which an intervention, procedure, or treatment regimen produces a desired effect when deployed in the field in routine circumstances.[2] When performed with an adequate sample size, randomization protects against selection bias and confounding variables.

Limitations of RCTs

There is, however, an increasing recognition of the limits of randomized controlled trials. Although RCTs can determine the effectiveness of an intervention in an experimental setting, different methods of research may be required to determine whether any harmful effects exist or to examine how patients experience any interventions they receive. In addition, randomized trials are expensive, not always feasible, and in some cases inappropriate to perform for ethical reasons.

EBMP involves tracking down the best external evidence with which to answer clinical questions. To determine the accuracy of a diagnostic test, cross-sectional studies of patients clinically suspected of harboring the relevant disorder is needed, not a randomized trial. When studying prognosis, even after a RCT, proper follow-up studies of patients assembled at a uniform early point in the clinical course of their disease is advisable. If no randomized trial has been conducted for an illness or complication, researchers and practitioners seek the next best external evidence and work from there.[3]

CATEGORIES OF RESEARCH DESIGNS

A basic understanding of common methods of research design is necessary to interpret the evidence presented in a research study. The *case report* describes an unexpected event to test whether it is a chance or regularly recurring phenomenon that needs further investigation. The report would have to address the likelihood of this phenomenon occurring by chance and if the event was predictable from any theoretical or empirical observation. The *uncontrolled case series* is a weightier case report since the event has occurred on numerous occasions; but, the need to address the same concerns as above applies. The rationale for conducting a *case-controlled study* is the potential to compare a selected endpoint in the study group to an external reference in the general population. However, it is important to evaluate the selection process to create the matched-control, that is, what biases could have influenced a person being designated a case or control and how representative were the subjects?

Studies using *birth certificates and health insurance claims* to generate data have become popular. Birth certificates provide data collected for civil and legal purposes, not for research. Administrative databases, that is, billing systems or state mandated record keeping structures were not created for epidemiological research.[4] Misclassification is common; some procedure claims are not accurately recorded and are obtained by nonmedical personnel; some procedures that are provided are not always billed and, therefore, do not appear on the record. As a result, important reproductive health-related information, such as type of birth defects and specific hypertension drug used in treatment, may not be routinely recorded; comorbidities such as diabetes are poorly recorded; and the type of diabetes is not specified (gestational diabetes mellitus [GDM], type 1 and type 2); in addition, level of glycemia, body mass index, and diabetic treatment employed is not available in the database for extraction; the type of medication is not specified providing only a general classification, that is, oral agent. As a result, researchers extracting data from these records have automatically speculated that glyburide had been administered to all patients when in fact there are currently several oral agents routinely used that could have been prescribed.[4,5] The veiled threat to junior faculty by their older colleagues to "publish or perish…" has often sanctioned the expedient method of obtaining data from administrative databases for epidemiologic research with the resultant "garbage in, garbage out" data obtained.[6]

Of the thousands of diabetes in pregnancy studies that have been published, the Cochrane Register of Clinical Trials has identified only 103 that were described as randomized trials. Of these, 28 studies were excluded. They failed to report information relevant to pregnancy compromised by diabetes and, in some cases, the publications reported on the same randomized trial. In general, the majority of proposed interventions can only achieve about 25%–35% reduction in a selected endpoint (i.e., macrosomia, shoulder dystocia). Therefore, the number of women who have to be recruited to prove that an intervention actually achieves its intended goal would have to be larger than the number currently reported in the majority of studies on diabetes in pregnancy.

The Effect of Research Methodology on Study Conclusions

The selection of the research design, the calculated sample size, and the level of glycemic control achieved in a given study are all potential confounders for study conclusions. The larger the sample size and the anticipated magnitude of the intervention, the greater the power, that is, the percent chance that the study will detect a significant difference when there is an actual difference. However, a study with a small sample size that suggests a statistical difference runs the risk of an *alpha error*, that is, the probability of a study showing a statistically significant difference when no real difference exists. In addition, the rate of a complication or the result of an intervention lower than expected by the acknowledged prevalence such as 50% anomalies with a small sample size raises the issue of selection bias. On the other hand, when study results do not reveal a difference in perinatal mortality, birth trauma, or shoulder dystocia, it does not mean that an important clinical difference does not exist. The failure of the study to provide evidence of a difference should not be confused with evidence of *no* difference. Therefore, a *beta error* is the probability of failing to show a statistically significant difference when a true difference exits (false negative).

Composite outcomes are those in which several individual outcomes are pooled to produce a single outcome. As the number of individual adverse outcomes decline in light of improved treatments, the use of composite outcomes can overcome this drop by combining different outcomes and enhancing the efficiency of a clinical trial. Outcome selection should obviously translate into a clinically important long-term outcome. It should be noted, however, that using composite outcomes does not necessarily lead to increased evidence of the benefit of a specified intervention. In addition, each element of the composite outcome needs to be presented as a secondary outcome so that practitioners can determine the efficacy of these outcomes in their clinical practices. When there are limited available resources for clinical trials, composite outcomes is an efficient and appropriate design solution that may also best reflect a real clinical outcome.[7]

It should be noted that even after an adequate sample size has been drawn, or the likelihood of making either an alpha or beta error are small, information regarding level of glycemic control throughout pregnancy, timing of diagnosis, and onset of therapy and methods of measuring levels of glycemic control can be serious confounders that alter the results of a study. See Chapters 11 and 12 in the text for appropriate examples and specific studies.

In reproductive literature, cohort, case-control and cross-sectional studies are common since many research questions cannot be addressed with an RCT. These observational studies are more prone to bias than a RCT. Goodman[8] suggests that, "…in identifying reasons for our scientific beliefs, we also want to know how strong a warrant they provide: how good are the reasons and how good must they be to compel us to revise our beliefs?" Therefore, once academicians and clinicians are convinced of the veracity of evidence, staying abreast of research in the field and/or one's medical specialty becomes a moral imperative with its foundations in both the Hippocratic Oath and the Oath of Maimonides. The contribution that Archie Cochrane made to the evolution of scientific methodology in the 1970s was to make the evidence less removed or disconnected from those people who should be using it to take care of sick people. Today, the Cochrane and Campbell Collaborations provide an evolving source of database tools and ideas to facilitate this enterprise.[9]

With the advent of the RCT and the ascendancy of the databases for retrieval of information, the research community sought a means to develop some strategy for sifting, organizing, collating, and arranging this knowledge of variable quality or reliability. One effort to address the problem was an attempt to rank "levels of evidence" according to different aspects of clinical practice, including therapy, prognosis, diagnosis, and so forth. The Oxford Center for Evidence-Based Medicine does this by stratifying levels of evidence based on degrees of methodological power and advantage based on the original efforts of the Canadian Task Force on the Periodic Health Examination (1979).[10] The US Preventive Services Task Force[11] (1996) has also adopted specific criteria for the evaluation of the quality of evidence.

EBMP involves a shift in paradigms. Historically, practitioners have relied primarily on their more experienced colleagues and supervisors, expert opinions, and their own personal experiences for professional guidance—subjective information sources that too often provided inaccurate and even harmful practice guidelines.[12] A charismatic spokesperson or "expert" may have tremendous influence on his peers, on policy makers, and/or the public. When all methods appear to be equally effective and those who depend on the information are not sure which direction to take, the vacuum is filled by an "expert" who has the oratorical and persuasive powers to say what *is* and what *is not* effective practice. The information, however, may be based on biased opinion and conflict of interest but not necessarily the facts. Consumers of research evidence need to ensure that the credentials of a seemingly notable scholar from a prestigious institution do not overawe them.

Advocates of EBMP explicitly reject the long-standing assumption that theory, traditional training, anecdotal experience or custom, consensus, or common sense alone provides sufficient guidance for effective decision making and professional practice. Intuition and unsystematic clinical expertise are insufficient grounds on which to make clinical decisions. On the other hand, the "value laden nature of clinical decisions" implies that we cannot rely on evidence alone… knowing the tools of evidence-based practice are necessary but not sufficient for delivering the highest quality of patient care.[13]

One of the origins of EBMP was the study of variations in practice and related outcomes.[14] Variations in practices suggest questions such as "Are they all equally effective?" "Are some more effective than others?" "Do some result in more harm than good?" Evidence has begun to indicate that there are significant differences among hospitals or doctors in a particular specialty. What you tend to find is a bell curve: a handful of teams with very poor outcomes for their patients, a handful with incredibly good results, and a great undistinguished middle. Acknowledging this bell curve is very distressing to practitioners since it contradicts the promise that they have made to patients who become seriously ill: that they can count on the medical system to give them their very best chance at life. We used to think that a doctor's ability depends mainly on science and skill. However, even doctors with great knowledge and technical skills can have mediocre results. What the best physicians do have, however, is a capacity to learn, whether from research data or clinical experience, and to do so faster than their average peers. What we are also learning, however, is that in addition to the above intellectual skills, the best practitioners often possess or strive to acquire more nebulous attributes such as aggressiveness, consistency, ingenuity, compassion, sensitive listening skills, and broad perspectives from the humanities and social sciences.[15]

A key characteristic of EBMP is to break down the division between research and practice, highlighting the importance of clinicians' ability to critically appraise research reviews and developing a technology to help them do so. It emphasizes clinician use of their scientific training and their judgment to interpret research and individualize patient care accordingly. EBMP is a guide for thinking about how decisions should be made in light of patients' preferences and clinicians' recommendations. Proponents of EBMP believe that findings from the most relevant scientific studies currently available should figure prominently in the practice decisions of clinicians. Judicious use of evidence involves balancing an assessment of the individual patient's unique characteristics, personal preferences, and life circumstances against relevant primary research findings or practice guideline recommendations for patient care.[14]

Misconceptions about EBMP including the criticisms that (1) it will replace or seek to replace practitioner judgment, (2) it leads to a "cookie cutter" approach to medical practice, and (3) it is too time consuming to be routinely employed in real-life practice settings also might discourage widespread adoption of EBMP.[16] EBMP should never evolve into rigid practice because effective interventions require that practitioners integrate their professional understandings of patient care with recommendations derived from the best external evidence and patients' preferences.[16] The practice calls for candid descriptions of limitations of research studies and use of research methods that critically test questions addressed. It also calls for systematic research reviews rather than reviews authored solely by self-declared "experts."

SYSTEMATIC REVIEWS: META-ANALYSIS

Meta-analysis is a statistical procedure for synthesizing research results across studies that address a common topic or issue. The term means to analyze "after or beyond" the original analysis. It is the analysis of analyses, completed on a collection of studies usually to draw general conclusions. A major achievement of EBMP has been the development of systematic reviews, methods by which researchers identify multiple studies on a topic, separate the best ones, and then critically analyze them to come up with a summary of the best available evidence. It is more than a quarter of a century since Gene Glass coined the term "*meta-analysis*" to refer to systematic reviews whose results from different primary studies are statistically combined into an overall estimate.[17]

Meta-analysis is qualitatively different from other traditional reviews. The purpose of meta-analysis is to estimate the size of treatment effects to aid clinical decision making. Another major goal is to generate hypotheses to be tested in new clinical trials. They are not always bigger, and their main aim is not simply to be comprehensive but to answer a specific question, apply stringent inclusion criteria to studies reviewed, appraise the quality of the studies included, and summarize them objectively. However, a meta-analysis is only as accurate as the data on which it is based. The reader must examine the inclusion and exclusion criteria carefully in the studies that are grouped for the meta-analysis. For example, a study that evaluated different treatment modalities in a RCT with only 22 patients would not meet the sample size or power requirements to be included in a meta-analysis.[18] In two other double-blind randomized trials, the authors evaluated the efficacy of low-dose aspirin to prevent preeclampsia. The first study with 34 women found that a significantly reduced incidence of pregnancy induced hypertension and preeclampsia.[19] The subsequent study recruited 471 GDM participants, 774 chronic hypertensive women, 688 patients with multifetal gestation, and 606 with preeclampsia during a previous pregnancy. The authors found that low-dose aspirin *did not* significantly reduce the incidence of preeclampsia or improve perinatal outcome.[20] These studies demonstrate the effect of sample size on alpha and beta errors in research reporting.

Ranking different types of evidence by their level of scientific support is guided by three principles: quality, quantity, and consistency.[21] Quality refers to how the individual studies collectively minimized bias; quantity addresses the number of studies, sample size, and magnitude of effect; and, consistency pertains to whether findings are similar under different study conditions using different population samples or comparable study designs.[21] The strength of the evidence offered by a meta-analysis depends on how well the review is conducted. The systematic review often involves the skills of several reviewers working independently to screen thousands of abstracts and studies.

However, the high profile of meta-analysis as a method of analysis in evidence-based medicine practice has led to several misconceptions about its purpose and methods.[22] Systematic reviews of nonrandomized studies are also common, and qualitative studies can be and often are included in meta-analysis as are case reports. The systematic review is a method for limiting bias. However, since the choice of which study designs to include is made by the reviewers, bias may sometimes be introduced.[23–25]

There is also a common myth that meta-analysis requires the adoption of a biomedical model of health. Systematic reviews do not have preferred biomedical models and that is why there are systematic reviews in such diverse disciplines as education, social work, and public policy. Reviews on the *Cochrane Database of Systematic Reviews* commonly include "quality of life" as an outcome variable alongside clinical indicators of the effects of interventions. The systematic review, in medicine and other disciplines, is an efficient and effective technique for testing hypotheses, summarizing results of existing studies and assessing the reliability and validity of studies.[25]

Many researchers as well as clinical practitioners mistakenly believe that meta-analysis always involves statistical synthesis. A major concern is the potential for combining studies that are too diverse in treatment interventions, subject selection, outcome measurements, and research design. When no single study provides the purported evidence, maybe fusing all inaccurate studies together will finally provide the elusive evidence! Some systematic reviews summarize studies by describing the methods and results while others use meta-analysis by converting the data from each study into common measurement scales and combining the studies statistically. Many reviews do not use meta-analysis since pooling studies without taking into account variations in study quality can bias the conclusions of the review.[26]

Finally, authors and consumers of systematic reviews need to recognize that these reviews do not necessarily produce definitive answers to health care issues. They often identify the need for additional primary studies and are the vehicle for demonstrating future directions for new research efforts.[25] This methodology is useful in identifying "what works" beyond the world of EBMP and may also provide a platform for the combined knowledge and skills of the major players in health care provision today.

Clinical Guidelines

Most guidelines are a fusion of clinical experience, expert opinion, and research evidence. When the process of creating a practice guideline utilizes valid and current research evidence in systematic reviews, this has the potential to be translated into clinical decision aids for optimized health outcomes for informed policy decision makers in managed care systems and educated clinicians who in turn educate patients. It has been argued, however, that practice guidelines are too often based on the consensus of "experts" rather than actual evidence. Practice guidelines and consensus statements have sprung up under the sponsorship of groups

in which the validity of the disseminated message and credibility of the distributing agent are not always positively related. When the principles of EBMP are applied to the creation of these guidelines, the potential limitations inherent in guideline development are mostly overcome.[27]

Who Are the "Players" in Evidence-Based Medical Practice?

Evidenced-based medical practice is as much about the knowledge and ethics of educators and researchers as it is about the ethics of practitioners and policy makers in managed care systems. The health care system faces challenges from the many players who are individually and/or collectively involved in the formulation of policy or as recipients of those decision-making processes. EBMP involves sharing responsibility among all interested players for decision making in a context of recognized uncertainty.

Patients want more effective communication with their care providers so that they can make informed choices. A striking characteristic of EBMP is the extent to which patients are involved in many different ways.[28,29] There is a contemporary emphasis to compare the values and preferences of patients with recommended medical protocols and their likely consequences as well as "personalizing" the evidence to fit a specific patient's life and health circumstances. There is also a movement to help patients develop critical appraisal skills that will facilitate more active participation in their health care. The term "evidence-based patient choice" emphasizes the importance of involving patients as autonomous participants who themselves carry out the required integration of information from diverse sources in making decisions that suit their values and needs.[30]

Another way in which patients are actively involved in their own care is recognizing their unique knowledge in relation to application of certain regimens. The experts in deciding whether a guideline is applicable to a given patient is the patient and providers not the researchers and academicians who critically appraise research findings. The differing expertise needed to prepare systematic reviews regarding the evidentiary base of a guideline and to identify implementation potential highlights the inappropriateness of researchers telling practitioners and patients what guidelines to use. In EBMP, patients are involved as informed participants regarding the evidentiary status of services. There is an attempt to promote candidness and clarity in place of secrecy and obscurity. EBMP requires searching for research findings related to important practice and policy decisions and sharing what is found (including nothing) with patients.

Medical educators and clinicians want scientific bases for determining "best practice" approaches in addition to the research and statistical tools to learn how to assess the results of studies to enhance patient care. However, they need to adapt a common sense approach to EBMP. This approach integrates individual clinical expertise with best available evidence (relevant studies discovered from a systematic search of the health care literature). Practicing evidence-based medicine implies not only clinical expertise (proficiency and judgment acquired through experience), but expertise in retrieving, interpreting, and applying the results of scientific studies, and in communicating the risks and benefits of different courses of action to patients. EBMP dictates that professional judgments and behavior be guided by two distinct but interdependent principles. First, whenever possible, practice should be grounded on prior findings that demonstrate empirically that certain actions performed with a particular type of patient are likely to produce predictable, beneficial, and effective results. Second, every patient over time should be individually evaluated to determine the extent to which the predicted results have been attained as a direct consequence of the practitioner's actions. Judicious use of evidence involves balancing an assessment of the individual patient's unique characteristics, personal preferences, and life circumstances against relevant primary research findings or practice guideline recommendations for patient care. EBMP draws on the results of systematic, rigorous, critical appraisal of research related to important practice questions such as, Is this assessment measure valid? Does this intervention do more good than harm? Efforts are made to prepare comprehensive, rigorous reviews of all research related to questions of effectiveness, prevention, screening (risk and prognosis), description and assessment, harm, and self-development.

An ultimate objective of EBMP is the practitioner's consideration of the veracity of the findings of a given piece of research and its applicability to his patient or collective patient population. He/she will need to (1) know how to read and critique research articles and (2) assess the degree to which an intervention has been empirically tested and found promising. To access, analyze, and apply research findings in diabetic studies, practitioners will need to understand why, by whom, and how research studies are conducted. Therefore, medical school and continuing medical education will need to teach and reinforce the study of research design—the overall framework for collecting data once the problem has been formulated. In addition, these institutions will need to teach how to read and interpret the data and what they mean. The main objective of this educational strategy will be to integrate individual clinical expertise with critical evaluation of evidence discovered from a systematic literature search to solve a problem.

Understanding what kind of study has been performed is a prerequisite to thoughtful reading of research. What is now known is that physicians, under the influence of pharmaceutical advertising and promotions, are much more impressionable than was originally believed.[31] Only studies with comparison groups allow investigators to assess possible causal associations, a fact often forgotten or ignored. Large amounts of poor data forestall any amount of good data. Lots of zeroes may look impressive in research findings yet they still amount to zero. Unfortunately, most physicians lack skills in evaluating studies for bias and relevancy. This can result in harmful consequences to patients and is one of the reasons the enthusiastic use of the anti-inflammatory drug Vioxx caused harm to so many patients.

Clinicians confront voluminous evidence about the clinical choices they face every day. To remedy the problem, many medical groups issue clinical practice guidelines: experts in a field sort through the reams of clinical research on a medical condition and pore over drug studies; they then publish summaries about what treatments work best so that physicians everywhere can offer the most appropriate, up-to-date care to their patients. While this sounds straightforward, the process can go awry. The recommendations issued recently by the American Association of Clinical Endocrinologists (AACE) for the treatment of diabetes elevated second- or third-line drugs to more prominent

positions in the prescribing hierarchy, rivaling once uncontested go-to medications life metformin, an inexpensive generic. They also emphasized the riskiness of established treatments like insulin and glyburide, which now carry yellow warning labels in the AACE summary. Several of the now promoted drugs are expensive newcomers that lack the track records of clinical effectiveness and safety by the older, potentially displaced treatments. Physicians were perhaps given more treatment choices for their patients, but the AACE recommendations could also have been influenced by drug manufacturers who helped finance the new guidelines. What has evolved is the establishment of guidelines for guidelines, that is, guideline recommendations by various organizations are rigorously and fairly depicted (Institute of Medicine 2011 report) and not tainted by financial ties to the pharmaceutical companies that could win or lose based on their content. Overall, there is need for better study design, execution, reporting, and scientific critical appraisal skills by researchers and health care decision making as well as the drug manufacturers responsible for sales and distribution. At the end of the day, medicine, like art, is a creative process, and very much a team effort.

Excellent health care practice should be inspired by love and guided by science; both are essential. If a professional practices scientifically without compassion, he/she becomes a robot. On the other hand, if a practitioner is compassionate but unscientific, his failure to adapt EBMP methods in light of the burgeoning databases of relevant empirical findings might marginalize his medical practice and relegate his patients to substandard professional interventions.

Researchers and Peer Review

Peer review is the main apparatus that research journals use to assess the quality of the many manuscripts competing for the few places available for publication. Journal editors solicit evaluations of submitted manuscripts from outside experts who remain anonymous to the authors by the process. The results of a review can consecrate or doom the progress of a particular course of research. Often the results of clinical trials influence whether they will actually be published. Most journals want to be the first to publish positive new results. Negative results may not always be reported and are also less likely to be published in prestigious journals.[32]

The role of journals as gatekeepers for the scientific record dates from the 17th century when the Royal Society's (Great Britain) council was instructed to review submissions to its *Philosophical Transactions*. Despite over 300 years of use, the pursuit of excellence in research has not been accompanied by a parallel pursuit in the evaluation of that excellence. Envisioned as a way to ease reviewers' inhibitions, the practice of using anonymous reviewers diminishes accountability. Journal editors and anonymous reviewers base decisions about manuscripts on questionable criteria and standards from a largely secretive process. Medical journals often do not include clear statements about their peer review process, while reviewers are rarely informed of their role description as reviewers. In addition, because of the massive number of manuscripts in need of review, fellows in training and any other convenient reader (knowledgeable or not in the specific field) are recruited to adjudicate a manuscript's quality for potential publication.

The system is error-prone. History has shown that great scientific discoveries have often been achieved with minimal support and despite the active hindrance by the discoverer's "peers." When Dr. Rose Yalow first submitted the manuscript on insulin assay for peer review, she received a resounding rejection. Needless to say, it was this work that would be recognized in the future and would be the basis for her receiving a Nobel Prize.

It is also not difficult to understand how conflict of interest and jealousy can undermine the peer review process. Researchers whose work challenges the status quo are a threat to those whose careers are entrenched in the paradigm of the day. New ideas can jeopardize special interest groups and the funding they receive to pursue traditional approaches. As a result, peer reviewers have often hindered or even sabotaged scientific breakthroughs. The flaws in the process reveal bias founded on intellectual positions, personal convictions, as well as biases related to ethnicity, nationality, gender, and status. The results of the evaluation process have produced occasionally foolish and frequently incorrect statements, a lack of accountability enhanced by anonymity, as well as often personally insulting remarks.

Opinions will differ between reformers and die-hard defenders of the current peer review system. However, if the scientific community is to enhance its credibility, the peer review process must embrace a sounder and properly validated basis, that is, oversight without imposition. It requires a priori that a potential reviewer recuse him/herself if he has a bias against the authors or minimal knowledge on the subject. The referee's role is to read a manuscript and "… look neither for something to criticize to prove his diligence and capability as a referee nor overlook or condone omissions or errors to prove his graciousness. He should bear in mind that he is rendering a service to the editor, in the manner of an expert witness."[33]

The quality and usefulness of a journal rests on the quality of the research submitted, its reviewers' evaluations, and the editor's critical judgment skills. To enhance the objectivity and quality of the process, the scientific community needs to make a concerted effort to select reviewers who are knowledgeable, provide constructive evaluation, and impede the natural biases inherent in the review system.

Peter Doshi,[34] recently of Johns Hopkins University, is on a mission to influence and encourage the world's largest pharmaceutical firms to open their records to outsiders in an effort to better understand the benefits and potential dangers of the drugs that billions of people take every day. He is trying to gain access to data from clinical trials and make them public. The current system is one in which the meager details of clinical trials are published in professional journals often by authors with financial affiliations to the companies whose drugs they are promoting. This is not only conflict of interest but also free commercial advertisement that may also be misleading. The efforts of Dr. Doshi and other activists have encouraged GlaxoSmithKline Pharmaceuticals to pledge to share detailed data from all global clinical trials conducted since 2000. If and when that data are eventually publicized, it would amount to more than 1000 clinical trials involving more than 90 drugs.

Another related issue to drug research arises when major drug companies export their scientific development to emerging markets such as China. Since 2006, 13 of the top 20 global

pharmaceutical firms have set up research and development centers in China because it is cheaper to do research there. Auditors found that researchers did not report the results of animal studies in a drug that was already being tested in humans. Animal studies can identify safety risks and are among the main factors drug companies use to decide whether to pursue human trials. In addition, workers at the research centers had not properly monitored clinical trials and paid hospitals and participating doctors and other hospital personnel fees based on the number of people enrolled in a study. It is to the credit of Glaxo that it audited its own research facility. However, it also demonstrates what can happen when a drug company rapidly expands its clinical research programs overseas without adequate quality controls.[35]

Managed care providers have historically played key roles in influencing the behaviors of both practitioners and patients. They believe that EBMP is critical to the success of their plans' clinical performance but there is concern among many that the application of evidence-based guidelines derived from systematic reviews may in some cases increase costs. How plans can incorporate evidence-based practice into medical management activities and the modification of these strategies is a current focus for managed care providers. Incentives incorporated into systems that reward more efficient health care delivery, reduce waste, and lower costs could someday resemble a system that celebrates the attributes of EBMP. Managed care appears to be evolving from its original structure and rationale in traditional medical practice approaches to utilization management to participation in an evidence-based culture. As more high-quality synthesis of information relevant to an organization and delivery of care become available, greater familiarity with the retrieval and evaluation of systematic reviews can help managers use these sources effectively. If this trend continues, the system can adapt creative ways of rewarding practitioners, hospitals, and consumer adherence to evidence-based, cost-effective performance.

THE FUTURE OF EVIDENCE-BASED MEDICAL PRACTICE

It was the best of times; it was the worst of times,

It was the age of wisdom; it was the age of foolishness,

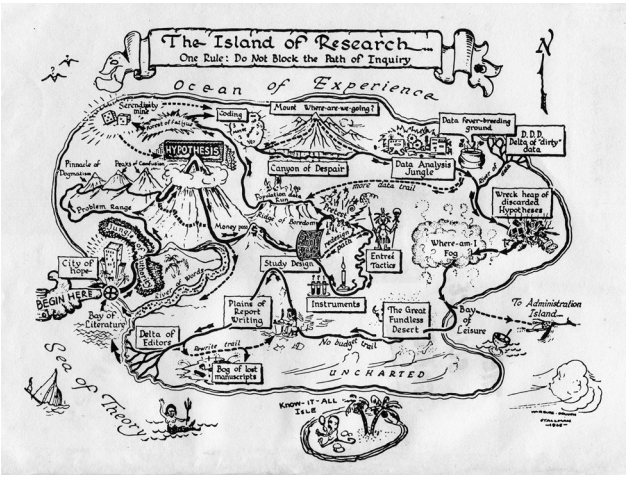
It was the epoch of belief; it was the epoch of incredulity,

It was the spring of hope; it was the winter of despair…

—Charles Dickens

With apologies to Charles Dickens, his words suggest the circumstances we currently face in the provision of health care. When historians of the future look back on the 21st century, we have no doubt that they will be impressed by the tremendous progress that has been made in science and medicine. A majority of our population has immediate access to effective health care services of all types provided by knowledgeable health care practitioners who know how to use them. However, at a time when we have more effective therapeutic tools than ever before, there are increasing impediments to the implementation and delivery of those tools. While millions have limited access to the essential care that is basic to everyday health and well-being, others lack the capacity to pay for this level of care, even if it were available. We spend vastly more on health care than any other nation in the world, yet analysis of our health status places us at the middle to the bottom among developed countries. In addition, despite all of the emphasis to advance our health care system, the medical community and physicians have yet to meaningfully step forward to lead improvements, or to advance medicine based on science rather than tradition and anecdote. If we recognize the shortcomings of "…the worst of times…" through thoughtful, informed, compassionate, and responsible leadership and participation, we can advance "…an epoch of belief…" And "…a spring of hope…" by capitalizing on the wonderful resources and potential of our health care system.

The successful promotion of EBMP can have a profound positive collective effect on health care if each of the partners (researchers/academicians, health care practitioners, patients, pharmaceutical companies, and managed care organizations) advance the principle that scientifically proven evidence-based medicine is the standard of quality and appropriateness in health care. Anecdotes, personal testimonials, and paid advertisements cannot define the gold standard. In this regard, health consumers and their physicians need the highest level of information for making health care decisions, that is, EBMP. "What we can do is maximize quality, minimize bias, manage uncertainty, and provide adequate support for those who have the task of ensuring that as our research moves forward, generating all kinds of evidence for clinical practice and policy, we do not lose sight of human health and suffering."[8]



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Pharmacologic Considerations Affecting Hypoglycemic Therapy During Pregnancy

3

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All things are poison, and nothing is without poison; only the dose permits something not to be poisonous.

—Paracelsus

Key Points

- Drug therapeutics can be significantly altered due to gestational changes in drug metabolism, disposition, pharmacokinetics, and pharmacodynamics.
- Placental drug transfer is difficult to assess and is influenced by the variable expression and activity of drug transporters.
- Oral hypoglycemic agents are subject to increased clearance during pregnancy, which calls for more aggressive dose titration and may limit their ability to achieve glycemic goals.
- Insulin analogs are widely used in diabetic pregnancies in the absence of specific pharmacokinetic data.

INTRODUCTION

Maternal physiology during pregnancy has evolved to favor development and growth of the placenta and fetus.[1] These adaptations may affect preexisting disease or result in pregnancy-specific disorders. Similarly, physiologic changes may alter the pharmacokinetics (PKs) or pharmacodynamics that determine drug dosing and effect. It follows that detailed pharmacologic information is required to adjust treatment strategies during pregnancy. Understanding both glucose metabolism and the gestation-specific pharmacology of hypoglycemic agents are necessary to individualize therapy so as to achieve tight glycemic control and improve outcomes. Unfortunately, most drug studies have excluded pregnant women, based on often-mistaken concerns regarding fetal risk. This "head in the sand" strategy does not, however, minimize either the use or risk of medications during pregnancy. Rather, over two thirds of women receive prescription drugs while pregnant with treatment and dosing strategies based on data from healthy male volunteers, and little adjustment for the complex physiology of pregnancy and its unique disease states.[2] This chapter reviews altered pharmacology during pregnancy that impacts therapeutics, specifically highlighting applications to hypoglycemic drugs.

Physiologic Changes Affecting Drug Pharmacokinetics in Pregnancy

Physiological adaptations to pregnancy, starting in the first trimester and gradually evolving through delivery and the puerperium, alter the absorption, distribution, and clearance of most drugs (Table 3-1).

Absorption

Gastrointestinal transit time is prolonged due to delayed gastric emptying along with both small and large bowel hypomotility during the second and third trimester, normalizing postpartum.[3] Decreased gastrointestinal motility might lead to higher oral bioavailability of slowly absorbed drugs and delayed peak plasma concentrations of rapidly absorbed drugs. Meanwhile, increased cardiac output and intestinal blood flow may allow for increased drug absorption overall. Gastric acid production is also decreased during pregnancy, whereas mucus secretion is increased, leading to an increase in gastric pH. Taken together, however, available data suggest that gastrointestinal changes have a minimal effect on the bioavailability and therapeutic effect of most oral drugs, especially with repeated dosing.

TABLE 3-1 Pregnancy-Induced Changes Affecting Drug Therapeutics

System	Parameter	Nonpregnant	Pregnant
Cardiovascular[135]	Cardiac output (L/min)	4.5	7.0
	Plasma volume (L)	2.6	3.5
	Extracellular fluid (L)	10–11	13–15
	Total body water (L)	31.8	38.6
Liver[32]	Portal vein blood flow (L/min)	1.25	1.92
	Hepatic artery blood flow (L/min)	0.57	1.06
Renal[30]	Glomerular filtration rate (mL/min)	97	144

Distribution

Cardiovascular changes during pregnancy include an increase in cardiac output starting in early pregnancy, plateauing by 16 weeks of gestation ~7 L/min and remaining elevated until delivery.[4] Pregnancy is also marked by an ~42% increase in plasma volume, to over 3.5 L at term, with parallel increases in total body water and in all body fluid compartments (see below).[4] Increased preload (due to increased blood volume and venous return), decreased afterload (due to decreased systemic vascular resistance), and an increase in maternal heart rate account for the rise in cardiac output. These changes, themselves, lead to increased organ specific blood flow and can facilitate drug absorption, distribution and clearance. Increased local blood flow and vasodilation are thought to facilitate drug absorption following intramuscular or subcutaneous drug delivery, although specific drug data, whether for insulin or other parenterally administered drugs, are lacking.

Maternal body fat expands by ~4 kg, increasing the volume of distribution for lipophilic drugs. However, little information is available to assess contributions by adipose tissue to altered drug disposition during pregnancy. Meanwhile, expanded extracellular volume and total body water likewise increase volume of distribution for hydrophilic drugs, leading to lower concentrations and increased clearances in the absence of offsetting adaptations. In many cases, plasma protein binding of drugs decreases during pregnancy due to reduced concentrations of both albumin and alpha 1-acid glycoprotein.[5–7] Decreased protein binding leads to higher concentrations of unbound drug, favoring distribution out of the vascular space into tissues and, for some drugs, to sites of hepatic metabolism. These changes can be clinically important in therapeutic monitoring of plasma drug concentrations, which usually do not specifically measure the concentration of free (unbound) drug. For example, phenytoin and tacrolimus efficacy and toxicity are related to unbound drug concentration in plasma. During pregnancy, both drugs exhibit an increased unbound fraction due to lower albumin concentrations; a lower red blood cell count amplifies this effect for tacrolimus.[8,9] A clinical dose titration strategy based on achieving whole blood concentrations in the therapeutic range can lead to increased free drug concentrations and possible toxicity. In pregnancy, a more rigorous, albeit cumbersome, strategy would be to monitor free drug concentrations and adjust drug dosing to maintain the unbound fraction within its therapeutic range.

Elimination

Renal drug elimination of most drugs or their metabolites depends on glomerular filtration and then on secretion or reabsorption by specific transporters expressed in renal tubular epithelial cells. Glomerular filtration rate (GFR) and effective renal plasma flow (RPF) both increase early in pregnancy, due to balanced afferent and efferent arteriolar vasodilation which is mediated by a signaling cascade including relaxin and nitric oxide.[10]. By mid-gestation, GFR increases by 40%–65%, and RPF by 50%–85%. Because the increment in RPF typically exceeds that in GFR, the filtration fraction (GFR/RPF) is reduced during pregnancy.[11] Creatinine production is unchanged in pregnancy but its clearance is increased due to increased filtration and secretion; resulting in lower levels of serum creatinine. Despite a uniform increase in GFR during pregnancy, differences in renal tubular transport (secretion or reabsorption) can result in differing effects on renally cleared drugs. For example, lithium clearance, which is almost exclusively via the kidneys, doubles during the third trimester compared to pre-pregnancy.[12] Conversely, atenolol clearance, also predominantly renal, is only increased by 12% during pregnancy.[13] Similarly, the clearance of digoxin (80% renal) is only increased by 21% during the third trimester when compared to postpartum.[14] Such variations in drug clearances limit generalization about the effect of pregnancy on renally eliminated drugs and point to important but understudied gestational changes in tubular transporters.

Drug transporters are widely expressed in all organs (Table 3-2). For example, intestinal luminal transporters can affect drug absorption from the GI tract, those in hepatic sinusoids determine drug uptake into hepatocytes where they may undergo biotransformation, transporters in biliary canaliculi govern secretion into bile and transporters on both the apical and basolateral surfaces of renal epithelial cells govern tubular secretion and reabsorption. Together, their distribution, substrate specificity, and activities are important determinants governing drug absorption, excretion and, in many cases, the extent of drug entry into target organs. Knowledge of drug transporter expression and function is necessary for a complete understanding of drug distribution and effect. In addition, several placental drug transporters have been identified, with potential effects on fetal drug exposure, including the family of multi-drug resistance associated protein (MRP). Phosphoglycoprotein (P-gp) and breast cancer resistance protein (BCRP) are the most studied so far. P-gp is expressed on the apical microvillous surface of syncytiotrophoblasts whereas

TABLE 3-2 Major Drug Transporters, Their Locations, and Common Substrates

Transporter	Organs/Cells	Selected Substrates	Selected Inhibitors
P-gp	Intestinal enterocytes, kidney proximal tubule, hepatocytes, brain endothelial cells, placenta	**Glyburide**, digoxin, loperamide, ritonavir	Verapamil, cyclosporine
BCRP	Intestinal enterocytes, hepatocytes, kidney proximal tubule, brain endothelial cells, placenta, mammary glands	**Glyburide**, statins, porphyrins, methotrexate	Oestrone, 17 β-estradiol
MRP2	Hepatocytes, kidney proximal tubule, enterocytes(luminal)	Glutathione and glucuronide conjugates, methotrexate	Cyclosporine, efavirenz
MRP3	Hepatocytes, kidney proximal tubule, enterocytes (basolateral)	**Glyburide**, Oestradiol 17 β-glucuronide, methotrexate, glucuronate conjugates	Delavirdine, efavirenz
MRP4	kidney proximal tubule, choroid plexus, hepatocytes, platelets	Furosemide, adefovir, tenofovir, methotrexate	Celecoxib, diclofenac
MDR3	Hepatocytes	Digoxin	Verapamil, cyclosporine
OAT1	Kidney proximal tubule, placenta	Acyclovir, zidovudine, lamivudine, adefovir, cidofovir	Probenecid, novobiocin
OAT3	Kidney proximal tubule, choroid plexus, blood-brain barrier	NSAIDs, cefaclor, ceftizoxime, furosemide	Probenecid, novobiocin
OCT1	Hepatocytes, endothelial cells	**Metformin**, N-methylpyridinium, pindolol, procainamide, ranitidine, amantadine	Quinine, quinidine, disopyramide
OCT2	Kidney proximal tubules, peripheral neurons	**Metformin**, N-methylpyridinium	Cimetidine, cetirizine, quinidine
OATP2B1	Hepatocytes, endothelial cells	**Glyburide**, statins, fexofenadine	Rifampicin, cyclosporine
MATE1	Kidney proximal tubule, liver, skeletal muscle	**Metformin**, N-methylpyridinium	Cimetidine, quinidine, procainamide
MATE2-K	Kidney proximal tubule	**Metformin**, N-methylpyridinium	Cimetidine, quinidine, pramipexole
PEPT1	Intestinal enterocytes, kidney proximal tubule	Cephalexin, cefadroxil, valacyclovir, enalapril, captopril	Glycyl-proline
PEPT2	kidney proximal tubule, choroid plexus, lung	Cephalexin, valacyclovir, enalapril, captopril	Zofenopril, fosinopril

Source: Adapted from International Transporter Consortium, et al.[145]

BCRP is mostly identified on the basolateral membrane and fetal blood vessels.[15–18] Efflux transporters on the apical membrane may protect the fetus by extruding harmful xenobiotics. Drug transporters may have wide substrate specificity (Table 3-2). P-gp substrates include endogenous cortisol, aldosterone, and bilirubin as well as drugs such as antibiotics, antiretrovirals, and steroids.[19,20] Substrates of BCRP include glyburide, antibiotics, antiretrovirals, calcium channel blockers, estrogen and prophyrins.[19,21,22] These transporters have a number of overlapping substrates for which they have differing affinities.[23,24]

A limited number of studies have examined the gestational changes of placental drug transporters. Most studies suggest that P-gp protein and its associated gene expression are elevated early in pregnancy and decrease near term.[25,26] Investigations of BCRP expression have yielded conflicting results with advancing gestation.[27,28] Pathophysiologic states may also alter transporter expression. P-gp and BCRP expression were each lower in placentas from women with preeclampsia compared to term placentas from uncomplicated pregnancies.[29] It is unknown whether transporter expression and activity are altered further in diabetic pregnancy.

Hepatic blood flow increases up to 160% during pregnancy, due to increases in cardiac output and in portal venous return.[30–32] The effect of increased hepatic flow on drug disposition varies with the ability of the liver to transport drugs from the circulation into hepatocytes. The extraction ratio (ER) refers to the proportion of a drug taken up from the hepatic arterial circulation into hepatocytes, making it available for subsequent elimination. For high ER drugs (e.g., morphine and propranolol), overall hepatic elimination is limited only by hepatic perfusion. By contrast, hepatic clearance of low ER drugs (e.g., diazepam, fluoxetine, or caffeine) is limited by intrinsic enzyme activity within hepatocytes and would be changed little by increased hepatic perfusion.

Beyond hepatic uptake, the major changes in hepatic drug clearance appear due to specific changes in the activity of drug metabolizing enzymes during pregnancy. Hepatic drug metabolism includes phase I (oxidation, reduction, or hydrolysis) reactions which introduce more polar or reactive moieties into drug molecules, followed in many cases by phase II (conjugation) reactions to glucuronic acid, sulfate, or other moieties which favor excretion into urine or bile. Oxidative phase I reactions, are predominantly carried out by the cytochrome P450 (CYP) family of enzymes that differ in their genetics and substrate specificity. The activities of CYP3A4 (50%–100%), CYP2A6 (54%), CYP2D6 (50%), and CYP2C9 (20%) are all increased during pregnancy.[33–37]. Changes in CYP3A4 activity increase the metabolism of drugs such as methadone, nifedipine, indinavir, and glyburide (see below). By contrast, CYP1A2 and CYP2C19 appear to undergo a gradual decrease in activity with advancing gestation,[38–40] albeit with uncertain effects on drug therapy. The activity of phase II enzymes, including Uridine 5'-Diphosphate Glucuronosyltransferases (UGTs), is also altered during pregnancy, with a 200% increase in UGT1A4 activity during the first and second trimesters, and 300% increase during the third trimester.[41] This change leads to lower concentrations of UGT1A4 substrates such as the anticonvulsant lamotrigine,[42] leading directly to poorer seizure control with advancing gestation in the absence of appropriate dose titration.[42] The effects of pregnancy on enzyme activity can also vary with maternal genotype. A recent study on the PK of nifedipine, used for tocolysis, noted differences in drug clearance due to genetic variability in a specific allele of the CYP3A5 gene.[43] Table 3-3 summarizes the most relevant hepatic drug metabolism enzymes, their substrates and the effects of pregnancy on enzyme activity.

Determinants of Placental Transfer, Fetal, and Neonatal Drug Exposure

Placental Transporters and Placental Drug Metabolism

Maternal and fetal circulations are separated by a layer of tissues composed of fetal endothelial cells and trophoblasts, the latter including villus stroma, cytotrophoblasts and syncytiotrophoblasts. With advancing gestation, the cytotrophoblast becomes discontinuous and the thickness of the syncytiotrophoblast layer decreases.[44] Perhaps surprisingly, several phase I and phase II drug metabolizing enzymes have been isolated from the placenta. The specific enzymes' quantity and activity vary as a function of placental development, gestational age and maternal health status.[45,46] Interestingly, most placental CYP enzymes exhibit decreased expression and activity with advancing gestation[47] so that studies in the term placenta may overestimate fetal exposure to maternally administered drugs earlier in pregnancy. While information on placental CYP activity is limited, new evidence suggests an active role in the metabolism of drugs, for example glyburide. Overall, the placenta appears to play a minor role in determining maternal disposition of glyburide, but may play a significant role in controlling fetal exposure to the drug and its metabolites, (see below).[48]

Drug permeation across the endothelial-syncytial membrane of the placenta can be influenced by numerous factors. Most drugs crossing the human placenta diffuse passively. As such, their transfer is determined by placental blood flow, drug concentration gradient, maternal and fetal pH, physiochemical properties of the compound (including charge and molecular weight) and the extent of protein binding.[49,50] By comparison, facilitated diffusion, phagocytosis, and pinocytosis are less significant routes of placental drug transfer.[47] However several drug transporters have also been identified in the placenta. Their location on the syncytiotrophoblast dictates a preferential direction of transport.[51] As such, apically located transporters are mostly involved in the efflux of substrates away from the fetal circulation whereas basally located transporters may facilitate drug transport into the fetal circulation. Interestingly, some transporters are located at both the apical and the basal membrane of the trophoblasts, and others exhibit bidirectional flow. P-glycoprotein (P-gp), MRP1 and the BCRP are highly expressed in placental tissue.[52] Located apically, they appear to have a major role in the efflux of compounds from the fetal to the maternal circulation.[53–55] Interestingly, most transporters have numerous substrates and more than one transporter may transfer a single compound. For example, glyburide efflux is mediated primarily by MRP1 (43%) and BCRP (25%), while metformin transport is predominantly due to P-gp (58%) and BCRP (25%).[56] When combinations therapies are used, they may lead to possible interaction and competition for efflux at the level of placental transporters.

STUDY STRATEGIES FOR PLACENTAL DRUG TRANSFER

In light of the ethical concerns and potential for fetal risk, different models have been developed to assess placental drug transfer. The choriocarcinoma-derived BeWo cell line[57] displays the

TABLE 3-3 Pregnancy-Induced Enzyme-Specific changes

Enzyme	Pregnancy-Induced Change	Potential Substrates in Obstetrics
CYP3A4[34,35,136,137]	Increased	**Glyburide**, nifedipine, methadone, indinavir
CYP2D6[136,138]	Increased	Metoprolol, dextromethorphan, paroxetine, duloxetine, fluoxetine, citalopram
CYP2C9[33,139]	Increased	**Glyburide**, NSAIDs, phenytoin, fluoxetine
CYP2C19[33,139]	Decreased	**Glyburide**, citalopram, diazepam, omeprazole, pantoprazole, propranolol
CYP1A2[38,39,136,140]	Decreased	Theophylline, clozapine, olanzapine, ondansetron, cyclobenzaprine
UGT1A4[141–143]	Increased	Lamotrigine
UGT1A1[41]	Increased	Acetaminophen
NAT2[39,40,144]	Decreased	Caffeine

morphological and biochemical characteristics of trophoblasts and is widely used to study trophoblast differentiation, placental metabolism, and substrate distribution across the trophoblast membrane. BeWo cells can form a confluent polarized monolayer in culture.[58] Experimentally, the monolayer is integrated into a membrane separating two chambers. Both chambers can be sampled for analysis allowing for assessment of transfer across the monolayer. While drug transporters have been identified in BeWo cells, their pattern differs from that in human placenta syncytiotrophoblasts.[59,60]

Animal models provide the advantage over cell culture systems of a complete physiological system where placental transfer can be assessed. However, large interspecies differences in placentation and pregnancy duration may impact the generalizability of any findings to humans.[15] For these reasons, mechanisms of placental drug transport, metabolism, and fetal toxicity are most often assessed in models of human origin. Various experimental approaches are available to assess placental drug transport in human ranging from umbilical cord sampling to explant trophoblastic tissue preparations and placental cotelydons. The methods, reviewed below, demonstrate different aspects of placental drug transport.

Fetal blood sampling and estimation of placental transfer can be achieved by collection of umbilical cord and maternal blood at the time of delivery, providing a measure of fetal/maternal concentration ratios which can be included in PK models along with results from repeated maternal sampling. This method is limited to a single sample at delivery collected at a variable duration from the last maternal dose. It also does not allow the assessment of placental metabolism, or of drug distribution in fetal tissues.

Perfusion of a single human placental cotelydon is an ex vivo model that is used to investigate the rate and mechanism of placental drug transfer.[61] The placental perfusion model has been used widely to evaluate placental transfer, metabolism, and the presence of overall active transport. It overcomes the ethical concerns for fetal risks in the setting of drug exposure and allows for human-specific conclusions. However, the model is sensitive to the gestational age when delivery occurred and perhaps on maternal disease. As such, the model provides no insight regarding placental transfer in the first trimester. Additionally, interindividual variation may occur and there is no standard for the number of placentas that have to be perfused to validate each experimental model.

Human trophoblast tissue preparations may also be used to study transport from the maternal circulation into the syncytiotrophoblast as well as placental metabolism across gestation.[62] This model requires careful consideration of the potential contribution of mesenchymal and endothelial cells to the metabolic process.[47] Membrane vesicles can be isolated from the apical or basal membrane of trophoblast allowing the study of transport mechanisms.[63,64] This model allows for characterization of individual transporters, but does not reflect the in vivo setting.

Oral Hypoglycemic Clinical Pharmacology During Pregnancy

Oral agents are first line therapy for type 2 diabetes in nonpregnant patients.[65] They are indicated during pregnancy when diet and exercise fail to achieve treatment goals and are favored by many over insulin in cases with mild hyperglycemia because of quicker patient learning, lower risk for hypoglycemia and higher compliance.

Glyburide

Glyburide, a second-generation oral sulfonylurea, acts by enhancing the secretion of insulin from pancreatic β-cells. Extrapancreatic effects may include improved tissue glucose utilization and reversal of early diabetic microangiopathy.[66] Clinically, it has been the preferred oral drug for the treatment of gestational diabetes mellitus (GDM). Glyburide increases insulin secretion in direct proportion to plasma glucose levels from 60 to 180 mg/dL, with lesser effect when glucose is less that 60 mg/dL,[67] though hypoglycemia remains a significant risk in the setting of overdose. When given as a single agent, peak plasma glyburide concentrations are achieved within four hours and absorption is unaffected by food. It is highly protein-bound (98%) and is extensively metabolized via multiple CYP enzymes then glucuronidated, facilitating subsequent renal and biliary excretion. Its elimination half-life is approximately 10 hours in nonpregnant adults and shorter in pregnancy due to increased clearance. A recent PK[68] study of glyburide in 40 women with GDM receiving glyburide monotherapy described 50% lower dose-adjusted plasma drug concentrations in pregnancy.[69] The differences in glyburide PK between pregnant and nonpregnant women were best explained by increased hepatic metabolism, given that unbound glyburide apparent oral clearance and formation clearance of its metabolite were each increased in pregnant subjects. Increased glyburide clearance likely results from the induction of CYP2C9, CYP3A, and/or CYP2C19, given that these are the enzymes involved in glyburide metabolism in vitro[70,71] and have been shown previously to be induced in pregnancy.[33,36,72]

While insulin secretion following a mixed meal was normalized in the glyburide PK-PD study, this was inadequate to compensate fully for insulin resistance[69] in some women. It remains unclear, therefore, whether higher than usual glyburide doses, titrated to achieve the same concentrations as in nonpregnant diabetic patients, would increase insulin secretion enough to achieve euglycemia. Indeed, there is a paucity of data, even in nonpregnant patients, as to whether glyburide has a "ceiling" effect or regarding the shape of its dose-response curve, with some studies suggesting little incremental benefit following increased doses.[73,74] Even with these uncertainties, it is clear that glyburide dosing should probably be more aggressive during pregnancy and should not be restricted to the doses used in nonpregnant type 2 diabetic patients. Further, given its short half-life in pregnancy, while it is unclear whether glyburide should be dosed more frequently, it is obvious that (steady state) therapeutic responses can be assessed within two days following each increase in dose, allowing clinicians to achieve control (or change therapy) more rapidly than in usual current practice.

The availability of more sensitive drug assays has revealed transplacental passage of glyburide, with fetal concentrations in fetal cord plasma approximately 70% of those in maternal plasma,[69] albeit with most levels being quite low in the single samples obtained at the time of delivery. In accord with limited drug exposures late in pregnancy, there is no evidence of either teratogenicity or fetal toxicity. Significantly, neonatal body

composition, cord insulin levels, and rates of hypoglycemia did not differ in offspring of diabetic gravidas treated with either glyburide or insulin.[75] Multiple placental efflux transporters, predominantly MRP1 with lesser contributions by BCRP and P-gp, serve to limit fetal exposure to maternally administered glyburide.[56,76] In addition, the placenta contributes to glyburide metabolism, though to a much lesser extent than the maternal liver. Placental CYPs have been shown to form all six known glyburide metabolites, two of which (M1 and M2b) possess hypoglycemic activity.[77] However, in the placenta, glyburide is predominantly transformed to M5 through the action of placental microsomal CYP19.[48,77] The formation of M5 in close proximity to the fetus could have clinical implications for fetal metabolite exposure. However, the pharmacologic and glycemic activities of M5 are yet to been determined.

Following delivery, while data are limited, glyburide is undetectable in breast milk, so that calculated maximum infant exposure would be less than 1.5% of the weight-adjusted maternal dose.[78] Blood glucose levels were normal in all three infants who were solely breast-fed in that study.[78]

Metformin

A biguanide, metformin is considered to be an insulin sensitizer that acts mainly to reduce hepatic glucose production by suppressing gluconeogenesis.[79,80] It also enhances peripheral glucose uptake. Since it does not increase insulin secretion, the risk of hypoglycemia is trivial. Oral bioavailability is approximately 50%, dose-related, and decreased when metformin is administered with meals. Peak metformin plasma concentrations in nonpregnant patients are achieved within three hours of oral administration for immediate release (IR) tablets and within seven hours for the extended release (ER) formulation.[81] The ER formulation expands to form a gelatinous mass; diffusion through this gel effects sustained absorption and allows once daily dosing with fewer gastrointestinal complaints than the IR formulation.[81]

In nonpregnant patients, the protein binding of metformin in plasma is negligible, and the drug does not undergo significant metabolism.[82] It is excreted unchanged by the kidneys via glomerular filtration and tubular secretion, the latter mediated by basolateral organic cation transporters (OCT) and luminal (apical) multidrug and toxin extrusion (MATE) transporters.[83] Metformin's elimination half-life in nonpregnant adults is approximately five to eight hours. Not surprisingly, its renal clearance is increased by approximately 50% and 30% in mid and late pregnancy, respectively.[84] Maximum drug concentrations were also significantly lower during pregnancy compared to postpartum.[84] Pregnancy-induced changes in renal clearance can be attributed to increased glomerular filtration or tubular secretion. In the pregnancy PK study, metformin oral clearance correlated better with net tubular secretion clearance than with creatinine clearance.[84] This is likely related to the high secretory clearance of metformin by OCT, primarily OCT2.[85,86] Enhanced net tubular secretion has been previously reported for digoxin[33] and amoxicillin[87] during pregnancy, but these mechanisms remain understudied in pregnancy. Interestingly, cimetidine is also both a substrate and inhibitor of OCT2, suggesting the possibility of drug-drug interactions with metformin in pregnancy.

Despite its widespread use, metformin's concentration-effect relationship has not been determined, making it unclear whether dose increases to account for increased clearance during pregnancy would result in improved glycemic control. Further, prolonged use reveals the slow accumulation of metformin in both liver and in red blood cells, making it difficult to determine the relevance, if any, of lower drug levels in plasma.[88] An additional consequence of this slow accumulation into its hepatic site of action is to limit the rapidity and confidence with which metformin dose can be titrated to quickly achieve glycemic control, since its effects will lag far behind changes in its plasma concentration. Finally, there are no data regarding the ER preparation in pregnancy, where changes in GI motility might be expected to minimize any benefits of this preparation.

As might be expected for a small, hydrophilic molecule with low protein binding, metformin crosses the placenta, albeit with low and variable fetal drug levels (maternal transfer rate 10%–16%).[84] However, metformin does not increase the risk of neonatal hypoglycemia if maternal glycemic control is achieved.[84] In addition, there have been no apparent long-term risks of using the drug in early gestation. A study assessing 126 infants at age 18 months born to 109 mothers who conceived and continued metformin during pregnancy found similar size and motor-social development in infants exposed to metformin compared to the non-exposed group.[89] More recently, the Metformin in Gestational diabetes: The Offspring Follow-Up study (MiG TOFU) compared outcomes following maternal treatment with metformin or insulin on the growth and body composition of their offspring.[90] Children exposed to metformin had larger measures of subcutaneous fat, but overall similar total body fat percentage and mass compared to children whose mothers received insulin.[90] While maternal outcomes were similar with metformin and insulin in the original study, these findings suggest the need for additional offspring follow-up to determine the long-term consequences of maternal treatment.

Three studies assessed transfer of metformin into breast milk; they all suggested that metformin is excreted into breast milk at very low levels.[91–93] The mean estimated infant dose as a percentage of the mother's weight-adjusted dose was 0.18%–0.65%.[91–93] In one study, blood glucose concentration measured four hours after feeding was within normal limits in all infants.[93] Another study found no differences in weight, height, or motor-social development at 3 and 6 months of age between 61 nursing and 50 formula-fed infants who had all been born to mothers treated with metformin throughout pregnancy for treatment of polycystic ovary syndrome.[94]

Insulin and Insulin Analog Clinical Pharmacology During Pregnancy

Exogenous insulin therapy attempts to mimic the profile of insulin in response to diet and metabolic demands in order to maintain euglycemia. In the absence of infusion pump therapy, treatment usually depends on the use of separate insulin analogs to mimic the basal secretion by the pancreas and the rapid β-cell response to meals. In healthy non-obese adults, endogenous insulin is secreted at a basal rate of 0.5–1 units per hour, resulting in plasma concentrations of 5–15 μU/mL in the fasting state.[95] Within 30–60 minutes of a meal, insulin levels increase rapidly to a peak of 60–80 μU/mL, then return to baseline approximately two-four hours later. The first phase of insulin secretion begins within two minutes of nutrient ingestion and lasts for 10–15 minutes. The second phase of prandial insulin secretion follows and is sustained until normoglycemia is restored.

This section will review the different insulin formulations, their pharmacologic properties and discuss placental transfer. Efficacy and safety of different insulin preparations are beyond the scope of this chapter and are addressed elsewhere.

Long-Acting Insulin Analogs

In patients receiving insulin injections, the role normally played by sustained pulsatile pancreatic secretion is replaced (imperfectly) by prolonged release of insulin from the depot site.

Neutral Protamine Hagedorn (NPH) insulin is a suspension of protamine and insulin in which low concentrations of zinc allow the protamine component to form crystals with insulin. The breakdown of protamine and/or dissipation of zinc following subcutaneous injection destabilize insulin hexamers and results in the slow release of dimers and monomers into the circulation. Monomeric and dimeric insulin are each biologically active. The slow release of NPH from its subcutaneous depot and the dissociation of hexamers determine the PK and PD profiles of this preparation. NPH has an onset of action one to two hours following an injection, an intermediate duration of action (14 ± 3 hours) and a peak approximately four hours after injection.[96] In a representative glucose-clamp study, significant interindividual variability was noted,[96] likely due to inadequate suspension prior to injection.[97] NPH is commonly administered twice daily.

Insulin glargine is formed by replacing asparagine with glycine in the α-chain and lengthening the β-chain by adding two arginines at the C terminus. These changes shift the isoelectric point from that of human insulin to a more neutral pH. Following injection, the solution forms microprecipitates that must dissolve before absorption can take place. Enzymatic removal of the two arginine amino acids, either at the injection site or in the circulation, liberates metabolically active insulin. By comparison, insulin detemir's formulation includes the addition of a fatty acid side chain, which results in hexamer stabilization and hexamer-hexamer interaction. Slow breakdown of hexamers leads to metabolically active products. Detemir is also highly protein bound (98.8%) in the interstitial tissues and plasma, which may contribute to its prolonged duration of action.[98] Detemir absorption is uniform, since it does not require re-suspension and does not form microprecipitates. Long-acting insulin analogs have an onset of action 90 minutes following injection, and a duration of action of 16–24 hours.[96,99] Their time-action profile is longer and flatter compared to NPH, allowing for once daily dosing.

Short-Acting Insulin Analogs

Short-acting formulations of insulin are meant to replace the postprandial insulin response. For this reason, they are usually administered close to meal intake.

The classic short-acting insulin is regular insulin. In solution, it exists as an equilibrium mixture of monomers, dimers, tetramers, and zinc-containing hexamers.[100] However, in pharmaceutical preparations, the hexamers predominate. The large molecular size the hexamers is thought to delay absorption following subcutaneous injection and the need for hexamer dissociation further delays drug action,[100] resulting in an onset of action at 30–60 minutes and a duration of action of~3–4 hours.

Rapid-acting analogs include insulin lispro, insulin aspart, and insulin glulisine. Their molecular structures include minor modifications in the end of the insulin β-chain, which serve to destabilize insulin hexamers.[101,102] Following injection, rapid dissociation to monomers and dimers allows more rapid absorption compared to human insulin.[101–104] PK studies performed in adults with type 1 diabetes reveal that peak plasma concentrations of rapid-acting analogs are approximately double that of human insulin and that the time needed to achieve peak concentrations is less than half that for human insulin.[101,103,105] As expected, once past the peak, rapid-acting analog concentration falls more rapidly compared to human insulin, reaching less that 20% of peak levels 4 hours after administration.[101,103,105] Overall, the total availability of all three rapid-acting analogs are comparable to that of human insulin, because the absorption and subsequent elimination of human insulin takes place over a longer period of time.[101,103,105] These findings lead to a longer total subcutaneous and whole-body residence time of human insulin compared to rapid-acting analogs. Trials comparing aspart and lispro analogs reveal few differences in blood glucose profiles, and the time of maximal reduction of plasma glucose (40–60 mins).[106–109] Studies on glulisine suggest a more rapid onset of action, especially in obese patients.[110,111] This may be due to an effect of the site of injection. Injections in the abdominal area produce the highest plasma insulin concentrations at the earliest time compared with injections in the arm, thighs, and buttocks; but without significantly altering overall glycemic control.[104,112] Overall, the rapid short-acting insulin formulations are comparable and they are usually administered 5–15 minutes before a meal.

Insulin Clearance

Despite the widespread use of insulin for glycemic control in pregnancies complicated by diabetes, PK data for different analogs are limited and most dosing strategies are based on studies in nonpregnant adults. Insulin PK studies are also hampered by the limited availability of methods to measure and compare absolute serum concentrations of different preparations.[113,114]

Insulin degradation is complex and incompletely understood. First, it is necessary to distinguish between endogenous insulin, which is cleared following secretion into the portal circulation and exogenous insulin, which is absorbed into the systemic circulation following subcutaneous injection.

The liver is the primary site of endogenous insulin clearance.[115,116] Approximately half of portal insulin is removed during its first-pass across the liver. Hepatic uptake and degradation of insulin is a receptor-mediated and nutrient-sensitive process.[117] In general, glucose ingestion increases hepatic insulin uptake, presumably due to signals from the gut, since intraportal glucose infusion does not have this effect. Several studies have suggested that the increase in circulating insulin in obesity and type 2 diabetes is due, at least in part, to a reduced hepatic clearance, although not all studies agree.[118,119] Others have suggested a correlation between hepatic insulin removal and hepatic insulin effects.[120,121]

Since insulin administered by subcutaneous injection escapes first-pass removal by the liver, the kidney has a more prominent role in this setting.[122] Insulin clearance by the kidney occurs by two mechanisms: glomerular filtration and proximal tubular reabsorption and degradation.[122] After entering the tubule lumen, more than 99% of the filtered insulin is reabsorbed by proximal tubule cells, primarily by endocytosis.[46] Relatively small amounts of

intact insulin are excreted in urine. The kidney also clears insulin from the postglomerular, peritubular circulation, also via receptor-mediated processes.[123,124]

Studies on insulin clearance in pregnancy are few; one noted a 24%–30% reduction in hepatic insulin extraction in women with type 1 DM.[125]

Insulin degradation by renal and hepatic cells follows internalization into endosomes and, in kidney, then into lysosomes.[126,127] Insulin not cleared by the liver or kidney is ultimately removed by other tissues. In fact, all insulin-sensitive cells are able to remove and degrade the hormone including skeletal muscle.

Placental Transfer of Insulin and Its Analogs

Whereas early in vitro studies suggested that insulin does not cross the placenta in humans,[128] a subsequent placental perfusion study suggested that a small amount of insulin (1%–5% of the maternal arterial concentration) is transferred to the fetal circulation,[129] with the results limited by concerns regarding assay specificity. Recent placental perfusion studies using glargine and detemir demonstrated negligible placental transfer and animal studies showed rates of teratogenicity and embryotoxicity similar to human insulin.[130,131] Similarly, placental perfusion studies on insulin lispro demonstrated minimal transfer of the drug into fetal circulation, which increased in a dose-dependent fashion when supratherapeutic concentrations were used.[132] Overall, placental transfer of insulin is likely inhibited by its large molecular weight, with minute amounts appearing in the fetal circulation. Some studies have suggested that transplacental transfer may occur in the form of insulin-antibody complexes.[133] In a recent letter to the editor, McCance et al. reviewed the association between insulin antibodies and insulin transfer in 97 pregnant women with diabetes.[134] Their results suggested that insulin antibodies are low at baseline and did not significantly increase during pregnancy when using either human insulin or insulin aspart. The study also failed to show increased placental transfer of insulin aspart, even in subjects with high levels of insulin antibodies.

CONCLUSION

Gestational changes in all of the processes regulating drug distribution and elimination can lead to dramatic changes in pharmacokinetics and pharmacodynamics, requiring dosing strategies that differ from those in nonpregnant patients. Our understanding of the PK and PD of hypoglycemic drugs in diabetic pregnancy remain limited. The complexities of drug metabolism, distribution, and elimination, including variations in enzymatic activity and transporter expression, should be subjects of future research. Both glyburide and metformin clearances are increased during pregnancy, leading to lower plasma levels and perhaps limiting their hypoglycemic effects. Even with our limited current knowledge, it should no longer be acceptable to extrapolate pharmacological data from men and nonpregnant women when treating pregnant women.

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Pharmacotherapy for Diabetes in Pregnancy

4

Critical Review of Fetal Safety

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Pharmacology is benefitted by the prepared mind…You need to know what you are looking for.

—Siddhartha Mukherjee

Key Points

- Despite common perceptions and case reports, the cumulative evidence today suggests that oral hypoglycemics are not major teratogenic agents in humans.
- Glyburide is safe and effective for gestational diabetes since it crosses poorly the placental barriers.
- Glyburide is probably actively pumped by the placenta from the fetal to the maternal side.
- Metformin appears to be safe for the fetus when used for either polycystic ovary syndrome, type 2 diabetes, or gestational diabetes.
- Insulin lispro is probably as safe for the fetus as "regular insulin."
- Aspart insulin appears safe for use in pregnancy.
- Detemir insulin appears safe for use in pregnancy.
- Glargine insulin does not cross the placenta except at high doses.

This chapter will focus on analysis of existing data on the safety of pharmacotherapy for diabetes in pregnancy. It is critical to acknowledge that in addition to evidence-based information of placental transfer of drugs and objective data on fetal safety, there is a substantial aspect commonly ignored by practitioners, that is, the way women themselves perceive fetal risk, whether real or inappropriately assumed.

Since the thalidomide incident, physicians and pregnant women alike react as if every drug is a potential human teratogen. In fact, a very limited number of medications have been proven teratogenic in humans when used in their recommended doses. None of them is a drug used in the treatment of diabetes mellitus, types 1 and 2 or gestational.

As a result of this teratogenic perception, pregnant women commonly avoid taking medications even for life-threatening conditions. Very often physicians will alert women to the potential but unproven teratogenic risks, but will not necessarily highlight the maternal and/or fetal risks of the untreated maternal condition.

Studying drugs during pregnancy requires special considerations because drug studies cannot involve pregnant volunteers and may only include pregnant patients when the drug is needed to treat an underlying disease. It is easier to justify clinical trials for drugs that are specific for diseases only encountered during pregnancy (e.g., magnesium sulfate for eclampsia, corticosteroids for fetal lung maturation) than for those conditions not found exclusively in pregnancy (e.g., drugs for hypertension, asthma, or diabetes) (Table 4-1). Yet, the latter may be as necessary as the former for pregnant women with pre-existing medical conditions, and may be as important for the well-being of the fetus (as an indirect result of the health status of the mother) as to make their use almost mandatory. Also, drugs need to be studied during pregnancy not only for maternal indications, but also for fetal indications (e.g., fetal supraventricular tachycardia).[1]

PREGNANCY-INDUCED PHARMACOKINETIC CHANGES

A variety of physiological changes occur in women during pregnancy, in particular the cardiovascular, gastrointestinal, and respiratory systems, the kidney and the liver. Gestational changes may affect virtually every aspect of the pharmacokinetics of drugs, namely

TABLE 4-1 Different Drug Uses in Pregnant Women

Category	Examples
Drugs that do not cross the placenta	Heparin, insulin
Drugs with limited placental transfer	Glibenclamide (glyburide)
Drugs that have no teratogenicity ortoxicity to the fetus	Methyldopa, penicillins, and metoclopramide
Drugs that are needed in an emergency where the life of the mother or the fetus is at risk	Magnesium sulfate, corticosteroids
Drugs that are needed to treat the fetus	Digoxin
Drugs that are needed to treat conditions in the mother that could lead to substantial morbidity if left untreated.	Insulin, heparin, and salbutamol (albuterol)

absorption, distribution, metabolism, and elimination.[2] The distribution volume of drugs is often affected, as is binding to proteins, filtration by the kidney, and enzyme metabolism in the liver. Drug absorption from the gastrointestinal tract is also altered, mainly as a consequence of increased transit time and decreased gastric acidity.[3]

Plasma albumin concentration tends to decrease in pregnancy[4] probably due to an increase in plasma volume[5] or variations in the rate of protein synthesis and catabolism. In contrast, other plasma proteins, such as α_1-acid glycoprotein, and total protein content remain mostly unchanged.[4] There is also a rise in cardiac output and redistribution of regional blood flow toward the uterus, kidneys, skin, and mammary glands from skeletal muscle. Changes have been demonstrated in hepatic enzyme activity that can have an important impact on drug clearance, mainly in cytochrome P450 (CYP). For example, there is an increase in P450 3A4 and decrease in 1A2.[3,6] Clearance rate may also be increased by the increase in glomerular filtration rate during pregnancy.[3]

PLACENTAL TRANSFER OF DRUGS

For centuries, it was believed that the placenta acts as a barrier that prevents transfer of molecules from the maternal circulation to the fetal compartment. With better techniques for sampling and measuring drugs, it has been shown that most small molecules do cross the placenta in a measurable way, sometimes achieving concentrations in fetal plasma as high as those in the maternal plasma. Similar to other epithelial barriers, transfer of drugs across the placenta is controlled by such factors as molecular weight (<1000D), PKa, lipophilicity, placental blood flow, and protein binding. Larger molecules (e.g., heparin, immunoglobulin M, dextran) do not cross, unless there is active transport.[7] For example, immunoglobulin G is actively transported across the placenta by a specific immunoglobulin receptor.[8]

The placenta displays several mechanisms to protect the fetus from the influence of xenobiotics, including specific transport systems (e.g., extruding drug pumps such as P-glycoprotein) and metabolizing enzymes (e.g., CYP isoenzymes).[9] Inhibition of these transport systems has been shown to alter the pharmacokinetics of several drugs (e.g., vincristine, cyclosporin, and digoxin), extruding them from the fetal circulation.[10]

Studying drugs in pregnancy is critical for several reasons. First, pregnant women often need drugs to treat conditions that can endanger the life of the fetus or their own. These drugs cannot be used optimally without proper clinical studies that define the pharmacokinetic and pharmacodynamic characteristics in this population and allow physicians to minimize toxicity and maximize efficacy. Second, this is a special population exhibiting unique characteristics not shared by any other, namely hosting a second human being that can be adversely affected by drugs taken by the mother. Hence, clinicians often find themselves going in circles. There is a clear need for drugs properly tested in pregnant women in order to use them safely, but they cannot be tested unless there are reassuring data about their safety during pregnancy!

There are, however, reasonable and practical ways to study drug safety in pregnancy. Importantly, more than half of all pregnancies are unplanned. Capturing drug use during the early part of these pregnancies and following them up to term can create large cohorts that can yield important data on fetal safety. Case control studies are also important to address fetal safety. These can provide a first glance on the basic characteristic of the drug in the pregnant population. Useful information about teratogenicity, adverse effects in the mother, and perinatal risk can be obtained and weighed in order to decide whether it might be safe to conduct trials with a given drug.

Preliminary pharmacokinetic information can be extracted from population studies that can be useful as a foundation for further studies. For most drugs, there is a wide body of pharmacokinetic data from the non-pregnant population that can serve as a guide for the design of future trials, especially if the different physiological variables that can alter the pharmacokinetics of the drug are taken into account. Cord blood sampling can be performed on neonates whose mothers are receiving the agent to be studied. Both cord blood and maternal concentrations can be established and collected in a centralized manner in order to derive population pharmacokinetic data. Moreover, many women are prescribed drugs they need in pregnancy, and there is no ethical hurdle in studying their pharmacokinetics.

In vitro studies, such as placental perfusion studies, can provide very useful insights into the pharmacological properties of the drug, some aspects of its pharmacokinetics and the characteristics of its placental passage. As discussed later in this chapter, this has proven to be of great value in the case of glibenclamide (glyburide) in gestational diabetes.[11]

Fourth, and ideally, drugs used during the second and third trimester should be studied with a design that allows the subject to serve as her own control (e.g., obtaining data serially during the second and third trimesters and then during the postpartum period).[3] The studies should take into account the physiological variations that occur in pregnant women in order to measure the differences in pharmacokinetic variables (such as changes in protein binding, distribution volume, metabolism, and half-life).[3] New drugs should not be commonly prescribed during the first trimester until proven safe, to minimize teratogenic risks. Finally, a comprehensive list of drugs potentially useful for pregnant

women with parallel medical conditions but that need to be better tested should be established in order to prioritize those that are potentially most effective and safe.

INSULIN USE IN PREGNANCY

Sulfonylurea drugs have been used sporadically to treat diabetes in pregnancy. However, the clinical belief that they have teratogenic potential, and the recognition that they can cross the placental barrier and appear in the fetal circulation, thus increasing the risk of neonatal hyperinsulinemic hypoglycemia, led to the virtual banning of their use in the pregnant population.[12,13] This left insulin, which is not appreciably able to cross the placenta due to its high molecular weight, as the only available drug for this condition, a fact that is reflected in several practice guidelines.[14,15] Nevertheless, there are several drawbacks to insulin therapy, and obtaining appropriate glycemic control in pregnant diabetic women is a major challenge, as discussed in several chapters in this volume.

There are data showing altered insulin pharmacodynamics during pregnancy[12] with a significantly lower insulin-mediated glucose disposal during pregnancy than after delivery. This can be explained by an increased insulin resistance mediated by placental hormones, primarily human placental lactogen. Insulin pharmacokinetics are not significantly altered by pregnancy, as no change in volume of distribution, clearance rate, and half-life could be found.[16]

Insulin therapy in pregnant women with gestational diabetes or type 2 diabetes may require several daily injections (up to four)[17] to achieve adequate normoglycemia, making compliance a critical issue.[18] Patients with gestational diabetes need to adjust to the new diagnosis as well as to the need for injections. Many women with type 2 diabetes may not have needed insulin prior to pregnancy, but now need one or a few daily doses of an oral drug in order to control glucose levels, making insulin injections even less palatable In addition, handling, stocking, and refrigerating injectable insulin are major problems in many developing countries.

Insulin is an anabolic drug that has been shown experimentally to cause macrosomia in animal fetuses with hyperinsulinemia in the absence of maternal or fetal hyperglycemia. Macrosomia increases the risk of fetal death, possibly due to hypoxia which may occur because of the increased oxygen demands by the macrosomic fetus.[19–21] Although insulin does not normally cross the placenta on its own at normal levels, it has been found to do so as insulin-antibody complexes, the amount of transfer being directly correlated with the amount of anti-insulin antibodies in the mother.[22,23] High levels of insulin in cord blood and amniotic fluid has been associated with the risk for neonatal macrosomia.[24,25] The use of human insulin (as opposed to porcine or bovine insulin) is believed to minimize the production of anti-insulin antibodies. Nevertheless, Balsells et al. observed anti-insulin antibody production in response to human insulin treatment in women with gestational diabetes.[26] These antibodies crossed the placenta, as they could be measured in cord blood in concentrations proportional to those in the maternal blood. Yet, the rate of adverse fetal outcome did not differ between the mothers with anti-insulin antibodies and controls. It is not known whether the presence of these antibodies promotes transplacental transport of insulin. A more recent study focusing on the relation between anti-insulin antibody levels and fetal outcome failed to find a correlation, even though placental passage of antibodies was again demonstrated.[23]

A fast-acting new form of insulin, insulin lispro, that can be injected immediately prior to meals (instead of 30 minutes before, as with regular insulin) has been tested in pregnant women with gestational diabetes, showing fewer hypoglycemic episodes with a similar level of metabolic control as regular insulin. Anti-insulin antibody levels were similar in the insulin lispro and the regular insulin group, and fetal or neonatal abnormalities were not observed.[27] An analysis of 635 pregnancies comparing insulin lispro and regular insulin found no increase in adverse outcomes in either gestational or pre-gestational diabetes.[28] Concerns have been raised about the increased risk for diabetic retinopathy observed in some patients treated with insulin lispro during pregnancy.[29] However, this has not been borne out in other studies.[28]

Insulin lispro is an insulin analog in which two amino acids, lysine and proline, on the β-chain are reversed. This results in a weaker tendency for self-association after subcutaneous injection, allowing for more rapid absorption of the insulin, faster onset, and shorter duration of action when compared with regular human insulin.[30,31]

Whereas early in vitro studies suggested that insulin does not cross the human placenta,[32,32a,32b] a subsequent placental perfusion study demonstrated that a small amount of human insulin, representing 1%–5% of the insulin concentration in the maternal artery, was transferred from the maternal to the fetal circulation.[33] The concentrations of insulin used in that experiment (59, 104, 448, and 1,198 μU/mL) would, based on an assumption of linear pharmacokinetics, correspond to peak serum insulin levels achieved after subcutaneous injection doses of ~14, 24, 104, and 278 units of insulin, respectively.[30] In addition, there is some evidence that beef-pork-insulin antibody complexes can cross the placenta leading to neonatal macrosomia.[34] Currently, there is limited information on the placental transfer of insulin lispro. The potential consequences of placental transfer include the risk of neonatal hyperinsulinemia and hypoglycemia. Animal studies suggest that hypoglycemia may cause teratogenesis.[35] There has been a recent report of congenital anomalies in the offspring of two women taking insulin lispro throughout pregnancy, despite optimal glycemic control.[36] However, no causal relation with insulin lispro was established. In studies with insulin lispro in pregnant rats and rabbits, no evidence of impaired fertility or harm to the fetuses was observed with doses as high as four times the average dose in humans.[37] The objective of the present study was to examine whether insulin lispro crosses the placenta using the technique of perfusing a human placental lobule in vitro.

PLACENTAL PERFUSION STUDIES WITH INSULIN LISPRO

Human placentae were obtained after vaginal or cesarean section delivery from uncomplicated term pregnancies and transported to the laboratory in heparinized ice-cold placental perfusion studies. Independent maternal and fetal circulations were established to a peripheral placental lobule within 30 min of the delivery of the infant, as previously described by our laboratory.[38,39] After

residual blood was cleared out of the vessels and intervillous space, a one hour "closed" (recirculated) circuit control period preceded the experimental period. During the control period, glucose and oxygen consumption and lactate and human chorionic gonadotrophin (hCG) production were measured to determine the baseline of these values for each experiment. All values measured were compared with those of the initial control period to ensure the maintained integrity of the placental preparation throughout the course of the perfusion experiment.

The physical integrity of the placental preparation was assessed by monitoring the stability of the fetal perfusion pressure and volume loss from the fetal reservoir; increases or decreases in pressure (>10 mmHg) and volume loss (>3 mL/h) were criteria for rejection of the preparation. After the one-hour control period, the perfusates in both the maternal and fetal circulations were replaced with fresh media, and insulin lispro at a concentration of 100 μU/mL was introduced into the maternal reservoir in four experiments. In four additional perfusion experiments, the concentrations of insulin lispro in the maternal circulation were 200, 580, and 1,000 μU/mL. The maternal circuit was "open" (non-recirculated) to deliver a constant concentration of drug to the lobule, while the fetal circuit was "closed" (recirculated).

Samples were obtained from the fetal reservoir and the maternal artery and vein every 20 minutes for the first two hours and subsequently every 30 minutes for the last three hours to measure insulin lispro, antipyrine, lactate, glucose, and hCG concentrations. Antipyrine is a freely diffusible flow-dependent transfer marker to which drug transfer is commonly compared. Oxygen, glucose consumption, and lactate production were measured during the perfusion to confirm that the tissue maintained its ability for energy metabolism. After four hours of perfusion with insulin lispo, the perfusates in both maternal and fetal reservoirs were replaced again with fresh media and circulations "closed" for a final one hour control period. All values measured were compared with those of the initial control period to ensure that the integrity of the preparation was maintained during perfusion.

Perfusate samples were kept at −20°C until analysis. The concentrations of insulin lispro were measured using the insulin lispro competitive-binding radioimmunoassay with overnight equilibrium incubation at room temperature (Linco Research, St. Charles, MO). This assay is highly specific for insulin lispro (100%) and has negligible cross-reactivity with native human insulin or proinsulin (<0.5%). Whereas the limit of quantitation is quoted at 2.5 μU/mL for a 100 μL sample using the manufacturers' kit, in blank samples of fetal buffer we measured levels of 5.89 μU/mL. Hence, we used this concentration to subtract from all apparent levels measured during the experiment in the fetal circulation; pH and pO_2 of the perfusate samples were measured by using a blood gas analyzer (Radiometer ABL 330; Radiometer, Copenhagen). The perfusate concentrations of lactate, glucose, ad hCG, as well as tissue hCG content were measured as described previously in our laboratory.[38] Antipyrine concentrations were determined spectrophotometrically.

The mean fetal concentration-time relation was plotted graphically. Least square regression analysis was used to study the relation between measured fetal drug concentration and time. The rate of appearance on the fetal circulation was calculated by the mean of the slope of insulin lispro appearance (in microunits) versus time (in minutes) and expressed as microunits per minute per grams of tissue. Comparisons among values were made using the Student's t-test.

In 11 women, 31–40 years of age, we measured serum insulin lispro levels 60 minutes after subcutaneous injection of a single lispro dose of 3–52 units. Of 11 women, nine were pregnant, two had gestational diabetes, five had type 1 diabetes and three had type 2 diabetes. One of nine women was in the first trimester, and the others were in the second or third trimester of pregnancy.

The mean mass of the perfused cotyledons was 11.8 ± 3.4 g. Placental glucose and oxygen consumption and oxygen delivery and transfer as indicators of metabolic viability of the placental tissue did not change significantly throughout the perfusion experiment.

Clinical Studies

Studies of insulin lispro have confirmed that postprandial glucose levels are lower using insulin lispro compared with regular human insulin, independent of HbA_{1c} level.[31] This may be important in pregnancy where high postprandial glucose levels can lead to fetal macrosomia.[40] Adjustment of insulin therapy in gestational diabetes to normalize postprandial glucose levels leads to normalized birth weight and lower rates of cesarean section.[41,42] There is also evidence that the use of insulin lispro is associated with a reduction in the frequency of hypoglycemia compared with regular human insulin.[43] In a meta-analysis of eight large clinical trials comparing insulin lispro to regular human insulin, the frequency of severe hypoglycemic episodes was lower in patients taking insulin lispro.[44] There is an increased risk of severe hypoglycemic episodes in pregnancy,[44] hence strategies to reduce this risk now include the use of insulin lispro. In a randomized double-blind trial of insulin lispro versus human regular insulin using a continuous subcutaneous insulin infusion, patients using insulin lispro had significantly lower HbA_{1c} levels.[45]

Clinically, lispro is used often during pregnancy for women with diabetes (pregestational and gestational), and it is considered safe in several clinical practice guidelines.[46]

Insulin Aspart

Insulin aspart is another short-acting insulin analogue where proline is replaced by aspartic acid.[47] It too gets absorbed twice as fast as regular insulin, has a higher concentration in the blood, but a shorter duration of action.

PLACENTAL TRANSFER

In one study, 13 cord blood samples whose mothers were taking aspart during pregnancy, were measured for insulin aspart, including four infants whose mothers received an IV infusion of insulin aspart during delivery.[48] No insulin aspart was detected in the cord blood suggesting that insulin aspart does not cross the placenta. There were no maternal levels of insulin aspart reported. Investigators also found that levels of insulin aspart-specific antibodies remained low in the mothers taking insulin aspart and in their infants, with no correlation between cord insulin antibodies and birthweight.

Clinical Studies

The largest randomized trial data to date comes from a study by Mathiesen et al.,[49] where 322 women with type 1 diabetes were randomized to receive either insulin aspart or regular insulin, along with NPH insulin during pregnancy.[49] While mean plasma glucose after breakfast was better in the aspart group, overall glycemic control, as measured by HbA1c, was similar in the two groups, There was a trend toward reduced rate of major hypoglycemia and nocturnal hypoglycemia, but these were not statistically significant. There was also a trend towards a lower rate of severe hypoglycemia in women who started insulin aspart preconception rather than during early pregnancy.[50] There was no difference in maternal or fetal outcomes.[49,51]

Insulin aspart is considered safe for use in pregnancy.[46,52]

Insulin Detemir

Insulin detemir is a long-acting insulin analogue with an 18–24 hour duration of action. It is produced by omitting amino acid threonine in position 30 of the β-chain of regular human insulin, and attaching a fatty acid to lysine on the same chain.[53]

PLACENTAL TRANSFER

To date, there have been no studies looking at the placental transfer of detemir insulin.

Clinical Studies

The largest randomized trial to date was done by Mathiesen et al., where 310 women with type 1 diabetes were randomized to use either insulin detemir or NPH insulin either up to 12 months prepregnancy, or during pregnancy at 8–12 weeks.[54] Glycemic control as measured by HbA1c was not different in the two groups although fasting glucose was significantly lower in the detemir group. Rates of major and minor hypoglycemia[53] as well as other maternal and fetal outcomes were also similar in the two groups.[55]

The Canadian Diabetes Association suggests "Detemir (level 2 evidence) may be used in women with pregestational diabetes as an alternative to NPH." The American Diabetes Association (ADA) and the National Institute for Health and Clinical Excellence (NICE) guidelines do not recommend the use of detemir, however, they have not been updated since the recent randomized trial of detemir in pregnancy.[46,52]

Insulin Glargine

Insulin glargine is a long-acting insulin analogue made by altering human regular insulin. Two arginine residues are added to the C-terminus of the beta-chain, and asparagine is replaced by glycerin on the α-chain.[53] These changes make onset of action slower and duration of action lasts up to 24 hours. Glargine has an increased affinity for the insulin-like growth factor I receptor (ref) and has been shown to be mitogenic in osteosarcoma cell lines. Because of this, clinicians have been reluctant to use glargine during pregnancy with the hypothetical fear that if glargine crossed the placenta it may cause increased growth in the fetus or even tumor formation. This has not been borne out.

Clinical Studies

There have been several cohort studies looking at the use of glargine during pregnancy. A meta-analysis of eight cohort studies of glargine use in women with diabetes in pregnancy (gestational diabetes and pregestational diabetes) was reported.[56] This included 331 women who used glargine during pregnancy compared with 371 women who used NPH insulin. There was no significant difference in several adverse perinatal outcomes between women using glargine and those using NPH during pregnancy.

Glargine and detemir use during pregnancy was compared head-to-head in a small retrospective cohort study of 67 women with type 1 diabetes who used detemir from conception and 46 women who used glargine.[57] Investigators did not find a significant difference between the groups in glycemic control or pregnancy outcomes except for a lower prevalence of large for gestational diabetes infants in women who took glargine.

Regarding clinical practice guidelines, the Canadian Diabetes Association suggests that glargine may be used in women with pregestational diabetes as an alternative to NPH (Grade C, Level 3). The ADA and NICE guidelines do not recommend the use of glargine in pregnancy.[52]

SULFONYLUREA DRUGS IN PREGNANCY

Sulfonylureas have been implicated as teratogens in animals and humans. Studies in rats and mice suggest that the first generation sulfonylureas, tolbutamide, and chlorpropamide are teratogenic in animals, although the role of altered maternal glucose metabolism could not be ruled out.[58,58a,59] There are anecdotal reports of malformations associated with exposure to sulfonylureas in humans,[13,60] but most of them have important limitations, namely the failure to consider the metabolic state of the mother as a teratogen.[61] On the other hand, a recent meta-analysis presented later in this chapter to show an increased teratogenic risk of sulfonylurea drugs during pregnancy[62] and a prospective cohort study of mothers with type 2 diabetes found that the only factors independently associated with an increased risk of malformations were maternal age at the onset of diabetes and metabolic control.[63] No relationship was found between treatment modalities (including drug therapy) and congenital malformations when glycemic control was taken into account.

There have been numerous case reports showing placental passage of first-generation sulfonylureas with adverse fetal consequences, primarily prolonged hypoglycemia of the newborn. The majority of these papers involve mostly the first-generation sulfonylureas (chlorpropamide and tolbutamide),[12,13,59,64–66] and also some newer agents. Chlorpropamide and tolbutamide were detected in umbilical cord blood in concentrations similar to those measured in the maternal blood.[21]

Miller et al. produced one of the first reports of placental transfer of tolbutamide in 1962.[65] In an experimental setting, they showed that maternal ingestion of one 500 mg dose of tolbutamide before delivery produced serum concentrations in the neonates ranging from 37–200 μmol/L, but had little effect on their glucose levels.[65] The lack of effect on the glycemic control of these neonates was explained by the absence of effect of the drug on their pancreatic β-cells due to the single administration, as opposed to the fetal β-cell hyperplasia observed with long-term administration in diabetic pregnant women.[66]

Nitowsky et al. administered experimentally a dose of tolbutamide to a 1-day-old healthy neonate and observed a half-life of 24.4 hours that decreased to 16 hours,[67] suggesting non-first-order

elimination kinetics. More recently, Christensen and Melander[64] reported the case of a premature baby whose mother had gestational diabetes treated with tolbutamide from the 24th week of gestation until delivery. The neonate had high levels of insulin relative to blood glucose, was large-for-gestational age, and had severe and long-standing hypoglycemia requiring intravenous glucose infusion and somatostatin for five days. Serum tolbutamide measurements in the baby showed elimination with zero-order kinetics during the first 90 hours of life, with a gradual increase of tolbutamide clearance afterward.[64] This points to ineffective elimination by CYP2C9 in neonates, in agreement with the developmental data available on this enzyme that suggests low expression during the first days of life.[68]

Kemball et al.[12] described four patients with prolonged symptomatic neonatal hypoglycemia associated with maternal sulfonylurea drug usage (three of chlorpropamide and one acetoxamide). They measured insulin and chlorpropamide levels in the blood of the babies and found that all four infants had evidence of increased and inappropriate insulin secretion, suggesting β-cell hyperplasia. Prolonged elimination of chlorpropamide was observed in the three infants who had transplacental exposure. Chlorpropamide could be measured up to 11 days after birth in these neonates, suggesting a similar prolongation of half-life as noted with tolbutamide. In two cases, exchange transfusion was required to remove chlorpropamide in order to speed recovery from hypoglycemia. Not surprisingly, this procedure had little efficacy, probably due to an increase in the distribution volume of the drug.[12]

Jackson reported high rates of neonatal mortality with gestational exposure to 500 mg chlorpropamide[69] although these figures were not universally accepted.[70] On the other hand, Sutherland et al. treated 19 pregnant diabetics with chlorpropamide and found no relation between the dose of chlorpropamide and fetal outcome. Intravenous glucose-tolerance tests performed on six infants shortly after birth showed faster insulin response and glucose disposition rates than among control babies, supporting β-cell hyperplasia due to chlorpropamide stimulation.[71]

Sutherland et al. followed 50 diabetic pregnant women who received chlorpropamide therapy and found no differences either in hypoglycemic episodes or macrosomia in their offspring when compared with a control group.[72] These reports point to a moderate to high placental transfer and slow elimination of the first generation sulfonylureas tolbutamide and chlorpropamide from the neonatal circulation. Pancreatic β-cell hyperplasia could be observed in most neonates, with variable degrees of clinical manifestations (from asymptomatic to prolonged hypoglycemia).

Few reports have addressed the effects of the newer generation sulfonylureas (glibenclamide, glipizide, and gliclazide) or repaglinide on the fetus. Coetzee and Jackson have reported on the use of glibenclamide (combined with metformin) during pregnancy both for gestational diabetes and type 2 diabetes. They managed over 600 women between 1974 and 1983, and found decreased perinatal morbidity compared with the control group and no cases of serious neonatal hypoglycemia.[73] No pharmacokinetic data were reported.

Langer et al. conducted a randomized controlled clinical trial comparing the use of glibenclamide and insulin in women with gestational diabetes. They found that glibenclamide and insulin were equally effective in achieving good glycemic control, and that perinatal outcomes were not significantly different.[11] Although mothers had therapeutic plasma concentrations of glibenclamide, the drug was undetectable in the cord blood of the matched neonates. This is a reassuring finding regarding the safety of glibenclamide in gestational diabetes.

There are several possible mechanisms for the absence of glibenclamide in the umbilical cord blood of the infants whose mothers had taken the drug. One may hypothesize that glibenclamide does not cross the placenta at all; however, this is difficult to justify from the physicochemical properties of this drug, as neither its pKa, lipid solubility, or molecular weight preclude it from being able to cross the placental barrier. Yet, Elliott et al. have shown that glibenclamide only minimally crossed the placenta in a single human cotyledon perfusion model.[74,75] This model has been widely used to evaluate human placental transfer of drugs and nutrients and can demonstrate placental passage independent of fetal metabolism and uptake.[73] In their in vitro studies, Elliott et al. showed that glibenclamide concentrations in the fetal compartment were marginal, even with maternal concentrations three or four times higher than peak therapeutic concentrations.[74,75] These data are in contrast with a previous experiment by Sivan et al. who showed in vivo that radiolabelled glibenclamide was capable of crossing the placenta in rats, and that radioactivity could be measured in the fetal tissues proportionally to the maternal blood concentration of the drug.[76] This discrepancy might be explained by high interspecies variability of placental tissue.

Data from a few studies suggest that drug transporters may play an important role. Glibenclamide has been shown to be a substrate for P-glycoprotein and P-glycoprotein induction by rifampicin[77] has been proposed as the reason for the decreased half-life and area under the plasma concentration-time curve of glibenclamide with prolonged administration of rifampicin. P-glycoprotein has been found in the human placenta[78] and its activity as an extruding drug pump has been proposed to influence the passage of several drugs.[10] Preliminary data have linked other potential drug transporters to glibenclamide pharmacokinetics (e.g., the bile salt export pump),[79,80] but no data about their placental expression are currently available. Other reasons for the poor placental transfer of glibenclamide may be its very high protein binding (99.8%) and relatively short elimination half-life (4–9 hours).[81] Because it is the free (unbound) drug that can cross the placenta, a very small fraction may be transferred within its short elimination half-life.

The study by Langer et al.[11] did not collect detailed pharmacokinetic data to shed more light on the pharmacokinetic-pharmacodynamic relationship of glibenclamide in this population. An important concern with the use of glibenclamide is the potential for drug interactions. As mentioned earlier, P-glyocprotein inhibition produces pharmacokinetic changes in disposition. Glibenclamide has been shown to both inhibit and be a substrate of P-glycoprotein[81,82] which could potentially lead to many different drug interactions in both the mother and the fetus.[10,83–85] This could eventually prove to be of importance, especially in complicated pregnancies where the mother has to take several concomitant medications.

The trial by Langer et al.[11] was conducted on patients who were otherwise healthy, gestational diabetes notwithstanding, which may not be the case with other pregnant women who could benefit from this drug. Glibenclamide may be of benefit in women

with type 2 diabetes, but awareness of concomitant medical conditions (e.g., renal disease) that can further alter the pharmacokinetic properties of the drug may be warranted.[86,87] A clinical study with careful stratification of the type 2 diabetic population should be considered to determine pharmacokinetic-pharmacodynamic relationships in pregnancy, based on available data from the non-pregnant population.[86,88–94]

Recently, a study by Hebert and colleagues have shown that, using a more sensitive method of detection, glyburide does cross to the fetus, however, fetal concentrations are much lower than maternal levels.[95] In a recent placental perfusion study, we showed that it is not P glycoprotein, but rather the breast cancer resistant protein (BCRP) transporter that effluxed the drug from the fetal to the placental circulation,[96] and this was corroborated by experimental studies.[97] The case of glibenclamide highlights the fact that a relatively small non-ionized and lipid-soluble molecule may cross the placenta marginally in vivo and that this could be predicted from in vitro pharmacokinetic models such as the placental perfusion model. The single cotyledon perfusion study has proved to be a valuable tool in the preclinical evaluation of drugs that could be of use in pregnancy. Still, better prognostic methods and algorithms are needed to be able to predict with higher confidence which drugs may not cross the placenta.

In view of the fact that infants of diabetic mothers have significant perinatal morbidity[97] that is often related to the degree of glycemic control,[98–102] the availability of glibenclamide as an option to treat gestational diabetes may be a welcome addition to the obstetrics formulary. Also, the results of Langer et al.[11] support the careful planning of further trials in order to expand the indication of oral hypoglycemic drugs to other populations, namely pregnant women with type 2 diabetes. The use of oral agents in women with type 2 diabetes would be of great benefit, since these patients tend to be of lower socioeconomic status and tend to belong to immigrant populations in developed countries. The high cost of insulin and syringes may preclude the use of insulin in many populations, especially those where type 2 diabetes has a high incidence (native populations, immigrants and in developing countries). Given the opportunity to use oral agents, compliance may also improve, leading to better glycemic control and lower perinatal morbidity.

The success of the clinical trial conducted by Langer et al.[11] prompts reflection on the scarcity of well-performed drug studies in the pregnant population. There seems to be a widespread perception that studying drugs in pregnant women carries the unacceptable risk of unpredictable and deleterious adverse effects in the fetus (e.g., teratogenicity). On the other hand, it is widely acceptable in the clinical arena to use drugs as needed, even if there are known risks, as long as it is done sporadically and not systematically (e.g., drugs used in emergency situations in pregnant women). Under these circumstances, the risk is not perceived in its right dimension and can be both over- and underestimated according to what happens to a particular patient. Systematic clinical studies of suitable drugs need to be performed, with the risks being carefully assessed and measured instead of officially denying the treatment to a population and then unofficially using the drug "as needed." Pregnant women take, on average, three to five prescriptions during the course of their pregnancies, excluding the commonly prescribed prenatal vitamins, iron supplements, and tocolytic drugs. The most commonly prescribed drugs fall into the therapeutic categories of antibiotics, analgesics, antiemetics, and narcotics. Most of these drugs have little or no clinical data in pregnant women.

Clinicians would often shudder at the thought of conducting a clinical study of an oral hypoglycemic drug during pregnancy, but still would use it in "special cases," as shown by a wealth of case reports and series. This paradox leads to a waste of very valuable data and to a distorted perception of risks. This in turn leads to misuse of important drugs, either denying them to a population that could gain great benefit from them, or using them in a potentially dangerous way, exposing that same population to excessive and often unperceived risks.

In order to be able to start clinical studies of a certain drug, every effort must be made to collect meaningful pharmacokinetic and pharmacodynamic data from previous use of the drug in other populations and in animals, and derive predictions from these parameters as well as precautions regarding adverse effects observed. More common use of in vitro testing of placental transfer of drugs should be incorporated as a routine stage of drug development.

FETAL SAFETY OF ORAL HYPOGLYCEMICS: A META-ANALYSIS

As mentioned above, oral hypoglycemic agents (OHAs) have been largely avoided in pregnancy due to concerns regarding their teratogenicity, coupled with their ability to induce fetal-neonatal hypoglycemia. Specific OHAs have been suggested as the cause of anomalies in human case reports and animal studies.[101–103] These primarily include cardiovascular (transposition of great vessels, ventricular septal defect, atrial septal defect, and patent ductus arteriosus), central nervous system (anencephaly, spina bifida, and hydrocephaly), and renal (agenesis and cystic kidneys) defects.[104,105] The reported increased risk of major malformations in women with diabetes is up to fourfold of a baseline risk of 1%–3% in those without diabetes. Glycemic control, however, has also been implicated as an etiological factor for congenital malformation in women with diabetes. Poor glycemic control is known to be associated with an increased number of malformations in individuals with insulin-dependent diabetes in a dose-dependent fashion.[106–109] Near normalization of glycemic control is associated with elimination of this increased risk.[107–110]

To date, the teratogenic potential of OHAs has not been addressed by a systematic review. This meta-analysis was aimed at examining the relationship between first-trimester exposure to OHAs, and congenital anomalies and/or neonatal mortality, accounting for the potential confounding effect of maternal glycemic control.[115]

A search of the literature was conducted using Medline (1966–2000), Embase (1980–2000), and the Cochrane database of systematic reviews, teratology texts, and bibliographies of retrieved papers and books. The keywords pregnancy, diabetes; diabetes mellitus; non-insulin dependent; and polycystic ovary syndrome were used to search for studies on the disease. The keyword OHAs (including sulfonylureas and biguanides) were used to search for studies on exposure. As well, the keywords abnormalities; drug-induced, pregnancy complications; neonatal diseases and abnormalities; infant mortality; and hypoglycemia were used to search for studies on the outcome. The keywords were exploded where possible.

The search was limited to human pregnancy and English language. Studies were included if they enrolled women with type 1 or type 2 diabetes mellitus, or gestational diabetes, reported on first-trimester exposure to any type of OHAs and reported on the incidence of either major malformations and/or neonatal death. Whether studies reported on glycemic control monitoring was noted. Other potential confounding variables abstracted were maternal age, weight, race, comorbidities (e.g., hypertension), and complications of labor and delivery. Uncontrolled studies, case reports or case series with less than six women, editorials, reviews and animal studies were excluded. All abstracts, titles, and, if necessary, full reports and bibliographies were reviewed by one reviewer and a random subset of 5% were also reviewed by a second reviewer. Based on this screening, studies were chosen for detailed review. Using structured data collection forms, data were extracted independently by each reviewer and disagreements resolved by consensus. Studies with the most comprehensive data were included if patient information was presented in duplicate reports.

Glycemic control was rated as "adequate" for the study group if one or more of the following criteria were met for the group mean: Hemoglobin A1c (HbA_{1c}) less than 8%, fasting blood glucose less than 6.7 mmol/L, random blood glucose less than 11.1 mmol/L, and/or two-hour postprandial blood glucose less than 11.1 mmol/L. If studies reported glycemic measurements above these cutoffs, glycemic control was considered to be "inadequate."

Data were entered into 2×2 tables. Peto odds ratios (95% CI) and risk differences were calculated using the Cochrane Review Manager software (Revman 4.1, Cochrane, Denmark). Risk differences were reported because of the rarity of major malformations and neonatal deaths, leading to a number of empty cells in the 2×2 odds ratio tables.

The literature search yielded 4376 citations on initial screening. Twenty-two reports were chosen for detailed review. Ten studies were considered to be eligible.[106–114] Studies were excluded if they had less than six subjects, no patients with first-trimester OHAs exposure, an unclear number of patients exposed to OHAs, data duplicated in other published studies or no control group. There was initial disagreement regarding whether three of the 22 studies chosen for detailed review merited inclusion. This was resolved by consensus.

The 10 studies reported on 471 women exposed to OHAs and 1344 women not exposed to OHAs. There were three prospective cohort studies, three retrospective cohorts, three case series, and one case-control study. Eight studies were conducted at a single center and two were multi-center studies. Cases and controls were recruited from obstetric and endocrine clinics, except for one study from South Africa in which the venue was not stated. Two studies had financial support from pharmaceutical companies, three were funded by national, university or diabetic association sources, and funding was not stated for five studies. In terms of the quality of studies, six were "poor" two were "fair", and two were "good".

Most women in the studies had type 2 diabetes. Women with type 1 diabetes, gestational diabetes (first diagnosed with diabetes in pregnancy), and impaired glucose tolerance were also present in some studies. The type of diabetes was not defined clearly in two studies. Three studies did not provide any demographic information for the women enrolled, and two studies did not differentiate between those exposed and not exposed to OHAs for the information (age, weight or race) that was provided. Mean parity was also not significantly different between groups in the two studies that reported this information (2.2 exposed, 1.9 control; 2.5 exposed, 2.3 control. One study provided information about alcohol, smoking or drug use (five of 147 OHAs exposed, 7.7 of 185 control), and medications (14 of 147 OHAs exposed, 13.7 of 185 control). However, details about what medications were used was not provided. Information on comorbidities was not provided by any studies.

With regard to glycemic control, three studies had "inadequate" glycemic control. However, there was no significant difference between OHAs-exposed and non-exposed groups, and there was no within-study differences. For instance, in one study, the monitoring method involved hyperglycemic symptoms, glycosuria and fasting blood glucose, where "good" control was defined as being symptom free, having minimal glycosuria and a fasting glucose that was normal or reduced from previous levels. The exposed and control groups had good control in 32% and 34% of patients, respectively. In one study monitoring HbA_{1c}, the level was reported to be between 8.8%± 2.7% for exposed versus 8.3%± 2.4% for the control group while in another study HbA_{1c} was 8.2%± 0.2% for both groups. Although glycemic control was stated to have been monitored in four other studies by postprandial, random or fasting glucose, or HbA_{1c}, the quality of the glycemic control could not be assessed because of incomplete or absent information.

The OHAs used varied in the studies and included chlorpropamide (eight), tolbutamide (six), glyburide (one), glipizide (two), acetohexamide (one), glibenclamide (three), metformin (five), and phenformin (three). Studies with multiple agents (sulfonylureas and biguanides) did not provide details about which specific drug(s) were associated with adverse neonatal outcome. Information about birth weight, gestational age at delivery, minor neonatal malformations, neonatal hypoglycemia, hypocalcemia, hyperglycemia, and other neonatal outcomes were rarely and inconsistently reported across studies and were not statistically analyzed. Information on maternal disease, such as pre-eclampsia and labor and delivery complications was not available in many studies. In one study, it was noted that the cesarean section rate was similar between groups, while another study commented on similar labor and delivery complications between groups.

Major malformations reported included cardiovascular (interatrial septum aneurysm, interventricular defect, atrial septal defect, patent ductus arteriosus, congenital heart block, Fallot's tetralogy, transposition of great vessels ventricular septal defect, aortic coarctation, central nervous system (spina bifida, cerebral diplegia, microcephalic anencephaly, encephalocele, hydrocephalus, skeletal (sacral dysgenesis, cleft palate, vertebral anomalies, gastrointestinal (Hirschsprung's disease, imperforate anus, stricture lower ileum, deficient diaphragm, choanal atresia and genitourinary (renal agenesis, polycystic kidneys, hypoplastic kidney malformations.

There was no significant difference in the rate of major malformations between those exposed to OHAs and those not exposed (n = 10 studies, odds ratio 1.05, 95% CI 0.65–1.70). The test for heterogeneity was significant (P = 0.05). The overall risk difference for major malformations between the exposed and control

groups was 0.00 (95% CI-0.03–0.03, $P = 0.35$). The rates of neonatal death did not differ significantly between groups ($n = 6$ studies, odds ratio 1.16, 95% CI 0.67–2.00) However, the results were statistically and graphically heterogeneous ($P = 0.0006$). The overall risk difference for neonatal death was –0.03 (95% CI-0.17–0.12) and the studies were heterogeneous ($P = 0.0002$).

We were unable to explain the heterogeneity in the results among the studies by accounting for glycemic control. The odds ratio between studies with glycemic control rating was not significantly different for major malformations (1.06, 95% CI 0.62–1.81; exposed 27 of 336, non-exposed 35 of 433). The odds ratio for major malformations of the three studies with "poor" glycemic control was also not significantly different, 0.93 (95% CI 0.51–1.70; exposed 20 of 202, non-exposed 29 of 262). For neonatal death, the odds ratio for the four studies reporting glycemic control was 2.19 (95% CI 1.17–4.09; 32 of 146 exposed, 20 of 176 non-exposed). The heterogeneity in the results was also not explained by the study quality. shows that in the analysis of major malformations including only studies with "good-fair" quality, the results were similar to the group in total; odds ratio 1.02 (95% CI 0.60–1.75; 26 of 288 exposed, 35 of 390 non-exposed) and risk difference 0.00 (95% CI-0.04–0.05; 26 of 288 exposed, 35 of 390 non-exposed). For complete references the reader should refer to the original paper.[62]

There was no significant difference in rate of major malformations or neonatal death among women with first-trimester exposure to OHAs when compared to non-exposed women. This finding was present even in the few studies that factored in glycemic control (albeit poor) for major malformations. However, P for heterogeneity was significant for odds ratio for overall major malformations and neonatal death, and for the risk difference for neonatal death. This suggests that care must be taken in interpreting the results because the combined studies were heterogeneous. There were no within-study or between-study differences identified for glycemic control to explain the heterogeneity. There was no significant difference between "poor" to "good-fair" quality studies. The heterogeneity may reflect different agents, patient populations and patient selection. In addition, the existing studies did not report on many characteristics that may cause heterogeneity, including smoking, alcohol intake, and body weight, among others.

Neonatal death was significantly increased in studies with reported glycemic control (which was poor). However, one of the four studies in this analysis had a high perinatal mortality rate attributable to poor glycemic control in the early phase of the study and later changed to a stricter regimen, making interpretation difficult. Another study had a high rate of neonatal death in the OHAs and insulin groups, suggesting perhaps a different standard of care at the time.

Individual studies have conflicting results regarding the safety of OHAs in pregnancy. Some report higher rates of major malformations in women exposed to OHAs. However, many studies have not found this to be the case. These studies are heterogeneous, using different agents and doses, and direct comparison has been difficult. Many studies did not take into consideration glycemic control and even in those that did the quality of the control is not readily evident. The randomized, controlled study by Langer et al.[11] has shown that glyburide use for gestational diabetes in the second and third trimester does not increase maternal or fetal complications compared with insulin. There was no difference in the incidence of macrosomia or neonatal hypoglycemia. Similarly, there was no significant difference in glycemic control between glyburide versus insulin.[11] Although this study did not include first-trimester exposure to OHAs and, therefore, does not discuss congenital malformations, it brings forward the notion of alternative methods of treatment with the focus on appropriate glycemic control.

There are a number of weaknesses in this systematic review. Most of the studies available were of poor quality, included multiple agents, and did not comment on type of drug or dosage used for any given malformation. Only studies that were published in English were included in the present review. Therefore, evidence published in other languages might have been missed. There are inherent weaknesses in meta-analyses of observational design, such as the incorporation of potential biases and flaws of individual studies, and reporting bias. Observational studies may lack information about important confounding variables (particularly, glycemic control in this study). Because more weight was assigned to one study in the present systematic review, potential biases inherent in it may have magnified the results. Even with preferential weighting toward studies with higher exposure/event rates, the effect of biases is potentially more serious in examining phenomena of low exposure rates (e.g., malformations).

An ideal trial to study the safety of OHAs in the first trimester of pregnancy would be randomized, controlled and double blinded. A group of patients with type 2 diabetes should be treated with an OHA to achieve optimal glycemic control. Rates of adverse effects should be compared with a matched control group not exposed to OHAs, but with the same glycemic control achievable with insulin. This is not currently feasible from a safety or ethical point of view because of the potential teratogenic effects of OHAs. Currently, there is an ongoing trial to randomize women with type 2 diabetes to receive metformin along with insulin or insulin and placebo during pregnancy (MiTy Trial). Women are randomized from 6 weeks gestational age. However, the study is not powered to detect congenital anomalies, and most women will likely enter the study after 14 weeks. Hence, to date, the best available information is from observational studies of patients who have been inadvertently exposed to OHAs and those treated with OHAs intentionally in a nonrandomized fashion.

Because of the weaknesses of the available data discussed above, this systemic review cannot be relied upon for clinical decision-making. If our findings were confirmed, they would have widespread implications. More women than ever with type 2 diabetes mellitus are of childbearing age and may become pregnant on OHAs. This study suggests that the risk of major malformations and/or neonatal death may not be as great as that previously reported, and it would appear that the use of OHAs in later pregnancy may be safe.[11] The use of OHAs in early pregnancy may warrant further evaluation, especially in environments where resources are insufficient to provide diabetic antenatal care with insulin and when OHA-exposed pregnancy is diagnosed after the first trimester. Until further information is available, women exposed to OHAs in early pregnancy should undergo detailed fetal structural scanning and receive close antepartum care.

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Diabetes and Related Metabolic States and the Placenta

5

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We live life forward BUT understand it backwards.

—Kierkegaard

Key Points

- Diabetes is associated with an increased likelihood of abnormal placental growth and development including markers such as abnormal placental shape, a feature commonly determined by the end of the first trimester.
- Diabetes may provide "competing" stimuli to the placenta (and by extension to the fetus). Histologically, these influences are reflected by highly variable villous histology ranging from hyperplastic (reflecting growth promoting effects) and accelerated maturation and other lesions reflecting diabetes associated vascular dysfunction.
- The effect of diabetes on the placenta may not parallel clinical glucose control.
- The effects of diabetes on immune function, to dysregulate inflammatory responses, may make infants of diabetic mothers more vulnerable to acute ascending infection than other age-matched fetuses.
- Fetal vascular pathology is reported to be common in infants of mothers with diabetes; this may be a primary mediator of brain damage in some infants.

INTRODUCTION

The increasing incidence and prevalence of diabetes is only paralleled by that of obesity. More than 35 years ago, Benirschke and Driscoll[1] dedicated 2.5 pages of their 475 page text to maternal diabetes mellitus; maternal obesity as an independent topic was not even listed in the index. However, as the prevalence of diabetes and obesity rises, the extent to which they contribute to adverse pregnancy outcome and the number and complexity of pathways by which diabetes and obesity contribute to adverse pregnancy outcomes have become clearer. Diabetes and obesity share a spectrum across which different combinations of growth-promoting and growth-restricting factors, as well as developmental and immunologic dysregulation, may alter growth trajectories of both fetus and placenta. In the decades since the St. Vincent's Declaration,[2] there remains considerable excess fetal morbidity and mortality associated with maternal diabetes and obesity attributable to increased rates of congenital abnormality due to teratogenic effects in the embryo, increased stillbirth rate, and increased macrosomia.[2,3] Effects span the full range of reproductive health issues, from preconception effects on ovarian function and lifelong health risks, both of which are covered elsewhere in greater detail in this book.

A growing concern is recognition that an abnormal fetal environment may cause long-term metabolic alteration of the individual and also its offspring,[3–7] what has been termed the "transgenerational passage of disease."[5] The growing prevalence of obesity may also be unmasking genetic tendencies to diabetes that may also impact fetal growth.[2,6] Manifestations of genetic conditions predisposing to diabetes and hypertension may vary with birth weight.[3] The increasing incidence of even nondiabetes-associated macrosomia may contribute to increases in the rates of diabetes and hypertension.[3] Although risks for individual pregnancies generally have declined over the recent decades, increased risks for poor outcome persist, apparently recalcitrant to treatment.[7] Given the increasing prevalence of diabetes and obesity, the overall number of pregnancies at risk is increasing.

The pathways linking diabetes and obesity clinically, and oxidative stress and inflammation pathologically, are numerous and are detailed elsewhere in this text. The working hypothesis underlying the following discussion is that diabetes and/or obesity may affect the maternal uterine environment by altering ovarian, endometrial, and/or uteroplacental vascular function via the mediators of oxidative stress and inflammation. However, the effect of diabetes on the fetoplacental environment may be more direct, altering the presence and distribution within the placenta of extracellular matrix molecules known to be important in normal placentation such as fibronectin[8] and affect trophoblast morphology in a mouse model of diabetes.[8] The placenta is the mediator of maternal and fetal metabolic pathways and is also affected by abnormal metabolism, in turn affecting the development of the fetus. Changes recognizable in the delivered placenta involve macroscopic, microscopic,

ultrastructural, and physiological changes. This review will focus on placental macroscopic (gross) and microscopic (histological) common but neither ubiquitous in nor specific for diabetes and/or obesity. A brief outline of important aspects of normal placental growth and development across gestation is followed by a review of evidence that diabetes and/or obesity may disturb those aspects of placental growth. Finally, the principal histopathology types and their associations with diabetes and/or obesity will be reviewed. We will present new analyses from a recent and comprehensive birth cohort that the placental dysfunction associated with maternal diabetes has its origins in the early conceptus.

NORMAL PLACENTAL GROWTH AND DEVELOPMENT

The placenta is the sole source of oxygen and nutrients for the fetus, and, therefore, is a principal determinant of fetal growth. Its growth is generally considered to be the *sine qua non* for the healthy growth of a euploid fetus. At the earliest stages of pregnancy, growth of the placenta requires sufficient ovarian function to produce the amounts of steroids needed to prepare the endometrium for pregnancy. Insulin has been shown to modulate ovarian steroidogenesis.[9] Once developed, the maternal endometrium must be receptive and the maternal uteroplacental vessels capable of accommodating the structural changes necessary for successful pregnancy. As noted by Boyd and Hamilton,[11] some of the early decidual changes of the endometrium can be simulated by exogenous supply of luteal phase steroid hormones. Insulin resistance may also modify the normal uterine receptivity of the late secretory phase; insulin-like growth factor–binding proteins have been recently implicated in the development of normal endometrial receptivity.[12]

The superficial subepithelial capillary network is a key site for early implantation. Histologically, this area appears to show increased permeability at the time of implantation,[10] which may increase the local concentrations of important nutrients. Endothelial dysfunctions associated with insulin resistance include decreased endothelium-dependent vasorelaxation, increased leukocyte–endothelial cell adhesion and vascular permeability, and the altered production of a variety of vasoactive substances that affect coagulation and extracellular matrix homeostasis.[13] Advanced glycation end products, products of oxidative stress that are present in higher levels in diabetes, act to quench nitric oxide activity, oxidize low-density lipoprotein, and trigger an inflammatory–proliferative process that contribute to propagation of inflammation.[14] Since the contraceptive effect of intrauterine devices is via induction of local inflammation,[15] diabetes, as a proinflammatory state, would be expected to have a negative impact on early pregnancy establishment.

Upon implantation, the interstitial invasion of the trophoblast begins. Within a week postconception, the embryo is partially embedded in the endometrium. Although there is endometrial cell death, there is no "disorderly" necrosis, despite obvious signs of tissue destruction[16]; the invasive cells are actively involved in the phagocytosis of maternal cell debris. Macrophage signaling, and hence macrophage regulation, is impaired in type 2 diabetes,[17] with potential negative effects on the decidual phagocytosis essential to normal early pregnancy establishment. Phagocytosis is intricately involved in the pathways leading to the respiratory burst, secretion of inflammatory mediators, and antigen presentation; early decidual pathology may set the conceptus up for later chronic placental inflammation.

By the time the trophoblast approaches the spiral arteries to initiate conversion, they have already lost their media and elastica, and the endothelium is only supported by a network of connective tissue fibers.[18] In the first trimester, the normal conceptus environment has low oxygen tension compared with other tissues and with the fetus and placenta later in gestation.[19] However, in diabetes, any "baseline" gestational oxidative stress may be exacerbated by diabetes-associated elevations in plasma glucose,[20] plasminogen activator inhibitor-1 expression,[21] and vascular dysfunction due to abnormal vascular endothelial growth factor levels.[22]

Placental growth and development will be discussed in terms of gross features that have been part of the standard gross placental examination since their institution in the Child Health and Development Study and the National Collaborative Perinatal Project (NCPP) by Dr. Benirschke in the late 1950s.[23] Standard placental growth measures used in those older birth cohorts and still in use today include the following:

1. Placental disk shape (qualitatively, often as round-oval versus "other")
2. Location of umbilical cord insertion site relative to the edge of the placental disk
3. Larger and smaller placental disk axes
4. Placental disk thickness (which is often not specified as average, minimum or maximum, or as recorded from a specific site such as the region of the chorionic plate of umbilical cord insertion)
5. Placental weight (generally trimmed of extraplacental membranes and umbilical cord and removal of nonadherent blood clot)

A functional measure, beta, will also be discussed in general and in specific analyses related to the maternal environment that underlies placental pathology in diabetes and obesity.

Placental Disk Shape

Up to eight weeks gestation, chorionic villi cover the entire chorionic sac. Villous atrophy forms the future extraplacental membranes; this is effectively completed by approximately 13 weeks gestation.[24] Benirschke and Kaufmann[25] acknowledge that an early infarct may also contribute to an irregular placental shape. The determination of placental shape is, therefore, an early gestational event, as has recently been predicted by an empiric model of vascular fractal growth[26] and by comparison of features of placentas measured at 11–14 weeks and subsequently at term.[27]

Location of Umbilical Cord Insertion Site Relative to the Edge of the Placental Disk

The umbilical cord insertion site on the chorionic disc marks the early confluence of principal chorionic vessels, formed during the second gestational month.[25] Uniform placental growth about the cord insertion site will result in a centrally inserted cord, but the conventional wisdom has been that if the placenta grows more in one direction than in others (so-called trophotropism),[25] the cord insertion site will be eccentric, marginal, or (at the extreme) velamentous. An alternative theory for eccentric cord insertions,

the "polarity theory" proposes that the embryo may be malpositioned oblique to the endometrium rather than facing the endometrium.[25] Our work clearly places cord insertion eccentricity as an early developmental feature[27] and one that, based on the distributions of locations at delivery, is amplified as gestation advances.[28] In other words, early displacements of cord insertions will be more marked as gestation advances.[28]

Larger and Smaller Placental Disk Axes

The lateral growth of the chorionic disc is to a large degree completed by 30–32 weeks gestation, growing laterally by invasion of decidual veins.[30] The chorionic disk surface arterial and venous networks and umbilical cord can be considered the "high-capacitance/low-resistance" parts of the fetal nutrient and oxygen exchange system. The determinants of chorionic surface vascular arborization remain speculative.

Placental Disk Thickness

The placental disk thickness is an indirect measure of the extent of villous branching (arborization), and the nutrient exchange surface of the placenta, essential to successful fetal growth. Progressive arborization of the villous stem vascular tree increases the thickness of the placental disk. There appears to be an optimal placental thickness that balances a healthy nutrient exchange surface with optimal maternal intervillous perfusion.[29] We have speculated that if the villous tree is too complex or too dense, intervillous perfusion may be more sluggish. Abnormally thick placentas have been strongly correlated with adverse pregnancy outcome.[31] This association may be due to abnormally large placental oxygen demands limiting the oxygen available to the fetus, abnormal intervillous stasis through an abnormally complex intervillous space, or both. The majority of placental growth in the third trimester is in the third dimension of thickness; therefore, placental thickness would mark later intrauterine environmental adequacy.[32]

Placental Weight

Although there are many variables that may modify the measured placental weight, from fixation techniques to the volume of intraplacental or intervillous blood retained in the placental disk, placental weight is clinically used to "explain" birth weight; the fetoplacental weight ratio, the ratio of birth weight to placental weight, changes normally across gestation as the placenta matures.

Placental Weight and Functional Inferences

It is reasonable that how the placental weight is "packaged" would affect its nutrient and oxygen exchange efficiency and change the birth weight resulting from the given placental mass.[29,33] For example, one placenta might have an oval chorionic disk measuring 16 × 14 cm and up to 3- to 4-cm thickness and a second might have a chorionic disk measuring 22 × 20 × 2 cm; both placentas could weigh 500 g, but the two placentas would have very different structures. The first with its small chorionic disk area would spread over a smaller endometrial surface and overlie a smaller number of uteroplacental vessels, compared with a larger disk. Our analyses demonstrated that gross placental shape measures had independent predictive value for simple measures like birth weight, in excess of that attributable to placental weight alone. In total, placental measures accounted for 39.1% of birth weight variation and each of the six measures of gross placental features had independent and significant effects on birth weight.[33] This study also demonstrated that effects of six maternal factors (age, height, weight, parity, socioeconomic status, and race) on birth weight were at least in part mediated via their effects on placental measures[33] and that maternal factors could be differentiated into those affecting chorionic plate area (parity), those affecting disk thickness (socioeconomic status), those affecting both (African American race), and those affecting neither (smoking). This is important because these different gross placental measures are conventionally considered to have different "critical periods of development,"[24,25,27,30,32,34] thus in theory influencing birth weight by different mechanisms at specific point(s) in gestation. We have also identified gender-specific associations of placental measures with fetoplacental efficiency using multivariate spline regression.[35] Female infants' birth to placental weight ratios (FPRs) were more "responsive" to changes in placental chorionic plate growth dimensions with a strongly monotonic positive effect on FPR, while the association of changing chorionic plate dimensions for a given placental weight had no significant association with the balance between fetal and placental growth ($P < 0.0001$).[35] That the male fetus tends to be larger relative to most placental measures of shape and size may result in relatively reduced placental reserve disadvantaging the male fetus when faced with other gestational stressors. Gender dimorphic fetal placental relations may moderate the apparently greater female resilience (and greater male vulnerability) to gestational (and lifelong) stressors.

It should be noted that birth weight and placental weight do not vary in a strictly linear manner. A theoretical justification for nonlinearity is well known as "Kleiber's Law" (Basal metabolic rate ~ αBody mass$^{\beta}$), where $\beta = 0.75$, a fractal dimension. At term, the scaling factor β estimated from the regression ln(placental weight) = $\alpha + \beta$[ln(birth weight)] is 0.78 + 0.02 (range 0.66–0.89), or 104% of the allometric exponent predicted in a supply limited fractal system, 0.75.[36,37] This supports both the use of placental weight as a proxy for fetal metabolic rate when other measures of fetal metabolic rate are not available, and the hypothesis that the fetal–placental unit functions as a fractal supply limited system.[26]

Calculating from our regression equation,[33] a "predicted birth weight given placental size and shape measures," we demonstrated that the ratio of the observed birth weight to the birth weight predicted (by regression analysis) was an independent predictor of age 7 body mass index (BMI) and age 7 diastolic blood pressure, the latter independent of effects of maternal prepregnancy BMI,[38] the association persisting after adjustment for many confounders but with differential effects between Caucasian and African American children. The differential effect of early life predictors by race has not been reported but is not unexpected given greater vulnerability of African Americans to adverse birth outcomes, hypertension, and obesity.

Placental Weight in Diabetes and Related Conditions

There is no abnormality of placental growth yet identified that is unique to diabetes or related maternal metabolic states. However, abnormalities of placental growth can be observed in diabetic pregnancy, and these abnormalities may both mark timing in pregnancy of diabetes-associated stress and may plausibly be

explained by effects of oxidative stress or inflammation in utero. In diabetes and related metabolic disorders, the negative effects of oxidative stress and inflammation operate on a substrate also subjected to abnormal signal promoting growth.

PLACENTAL DISK SHAPE

The normal placental disk shape is round-oval, but chorionic disk outlines may be very irregular. The initial lateral spread of the placenta in the uterus may be irregular if the uterine environment is variably permissive of placental implantation and growth. Alternatively, an initially normal single placental lobe may be broken up into multiple islands or multiple lobes by placental infarct. Naeye lists "antecedents to the development of a bipartite or tripartite placenta" to include maternal smoking during pregnancy, maternal age ≥ 35 years, excessive vomiting in the first trimester, *diabetes mellitus*, parent or sibling with seizure disorder, and pregnancy outcomes such as preterm birth and neurological abnormalities at 7 years of age, but not fetal growth retardation, stillbirth, or neonatal deaths.[34] Naeye lists antecedents to the development of "irregularly shaped placenta" to include immunization or infection during the first trimester, smoking in pregnancy, excessive first trimester vomiting, *nondiabetic gestational acetonuria*, age ≥ 35 years, and preeclampsia.[34]

Given our current understanding of how diabetes works through inflammation and oxidative stress, the association of abnormal placental shapes with diabetes makes sense and, furthermore, suggests deleterious effects on the intrauterine environment dating from early in gestation.[27] Placental shape, albeit an early determined event, has persisting reliable negative effects on both achieved placental weight and the birth weight predicted from a given placental weight.[29,33]

Location of Umbilical Cord Insertion Site Relative to the Edge of the Placental Disk

Naeye[34] also described antecedents to the development of marginal and velamentous umbilical cord insertions. Marginal cord insertion was associated with *maternal acetonuria during the first trimester, diabetes mellitus*, twins, major fetal malformations, placental growth retardation, and unevenly accelerated villus maturation. Antecedents for the development of velamentous cord insertion included maternal smoking, *diabetes mellitus*, congenital fetal syndromes, and placenta growth retardation. Of interest, velamentous cord insertion was associated with preterm birth and increased risk of neurological abnormalities at seven years, specifically hyperactivity syndromes.

At birth, both marginal and velamentous umbilical cords are mechanically vulnerable. Marginal umbilical cord insertion can become destabilized after membrane rupture when there is loss of the intraamniotic tension at the junction of the membranes with the chorionic disk that keeps that angle open. Velamentous umbilical cord insertion is mechanically vulnerable even before the membrane rupture due to increased risk of umbilical cord and/or chorionic vessel mechanical compromise. This is due to their location on the firm myometrial surface rather than the chorionic plate, inflated by the normally gentle maternal intervillous perfusion.

The intrauterine pathophysiology of diabetes and related metabolic pathologies would be an ideal setup for the types of placental growth asymmetry that result in eccentric or more perilous marginal or velamentous cord insertion sites. Diabetes is a risk factor for single umbilical artery,[39] suggesting that maternally derived vascular dysfunction effects may be translated to the fetoplacental compartment and not be confined to the uterine environment.

Larger and Smaller Placental Disk Diameters

When the placenta is irregularly shaped, measurement of disk diameters is more problematic. Both interobserver and intraobserver variations may occur; it may simply be difficult to choose a single pair of diameters to describe complex shapes. A single larger and smaller diameter simply do not capture the same amount of information about chorionic disk growth as those diameters do in a round or oval placenta; they are less valid. Measures that are differentially reliable and differentially valid, and work worst (are least reliable and least valid) in the most abnormally shaped placentas, are poor measures. A larger and smaller diameter does not capture the common complexity of placental chorionic surface growth. Again, gradients and nonuniformity within the uterine environment would reasonably predispose to abnormal placental shape; thus, standard placental measures of a single larger and a single smaller diameter would be less reliable and less valid measures for diabetic pregnancies.

Placental Disk Thickness

Naeye[40] also lists antecedents to the development of unusually thin placentas (less than 2 cm at full term) and unusually thick placentas (>3 cm at full term). The cutoffs are based on the distributions of placental thickness in the NCPP, a large government-sponsored birth cohort also from the late 1950s to early 1960s. He reported that abnormally thick placentas were more common in tall and *obese* mothers, mothers with *diabetes*, and in cases of fetal growth restriction and stillbirth.

Placental thickness in diabetes appears to be related to the considerable proliferative activity of the trophoblast but it is also due in some part to unusually prominent cytotrophoblasts and "voluminous" stromal cells.[41] Ogino and Redline[42] have suggested that increased capillary tortuosity (suggesting capillary proliferation) is also associated with maternal diabetes. Thus, there is evidence that increases in all villous compartments (strophoblast, stroma, and capillaries) may contribute to increased placental thickness. Placental thickness in the normal placenta tends to be uniform, consistent with a uniform intrauterine environment and equally permissive of villous arborization. However, diabetic pregnancies are at an increased risk for maternal vascular compromise, even when there is comparatively mild impairment of glucose metabolism.[43] Benirschke and Kaufmann[41] also note the marked variation of villous histology within any one placenta, and among groups of women classified as to the clinical severity of their diabetic disease. Maternal uteroplacental pathology is associated with reduced placental thickness due to decreased villous growth[27,44] and with reduced placental vascular growth factor levels.[45] Vascular pathology is, as mentioned, a complication of diabetes. The push and pull of growth-promoting and growth-limiting factors can be played out in the development of markedly variable placental thickness. As with large and smaller diameters, a single measure of placental thickness in the diabetic placenta, at risk for marked variability for

the reasons stated, may be particularly poor, compared to placentas growing in a more uniform intrauterine environment or less "complicated" uterine environment.

After adjusting for the effects of other placental measures, increasing placental thickness has a negative effect on birth weight for a given placental weight. We have found that the placental thickness–birth weight relationship is monotonic and positive in slope until placental thickness approaches 4 cm. After this, while placental weight continues to rise and placental thickness increases, the predicted birth weight drops precipitously. Abnormally low fetal weight for placental weight is characteristic of both obesity[46] and even in comparatively mild (diet-controlled) gestational diabetes.[47] It is not surprising that Lao et al.[47] and Lao and Ho[48] found abnormal fetoplacental weight ratios to be associated with increased perinatal morbidity in diabetic pregnancies.

Placental Weight

In the NCPP, the most common correlates of a placenta at greater than the 90th weight percentile were villous edema, *maternal diabetes mellitus*, severe maternal anemia, fetal anemia, congenital syphilis, large intervillous thrombi, and large subchorionic clot. Naeye suggested that when the placenta is large in the context of diabetes mellitus, the placental villi are histologically abnormally large, rather than merely swollen by edema.[41] In general, investigators have confirmed that although both the baby and the placenta tend to be large in maternal diabetes, the placenta is disproportionately so, resulting in a reduced fetal to placental weight ratio. As discussed briefly earlier, in a large study of 1472 consecutive singleton pregnancies with gestational diabetes, an abnormal fetal to placental weight ratio was found in 400 (27.2%). The abnormal ratio resulted from increased placental weight rather than the decreased birth weight. After adjusting for the effects of preterm birth and vaginal delivery, an abnormal fetal to placental weight ratio was still associated with a low Apgar score, respiratory complications, and treatment for infection.[49] Evers et al.[49] suggested that an increase in relative placental weight may protect the fetus from asphyxia; in fact, a relatively low placental weight in large-for-gestational-age (LGA) pregnancy was found in three of the four cases of perinatal death. These observations were refined by Makhseed et al.[50] who were able to attribute failure to achieve an increased placental and/or birth weight to the presence of maternal vascular disease. Lesions that can be interpreted as chronic fetal hypoxia in the relatively larger placentas of cases of gestational diabetes compared to controls.[51]

We have extensively published on a large modern birth cohort in which digital images were collected with allowed capture of very detailed and precise geometric and other shape-related quantities, and could be compared with a wide range of data collected during pregnancy.[52] We looked at our measure of placental functional efficiency, β, and disk thickness and its variability, two factors repeatedly identified as abnormal in association with maternal diabetes and obesity. Univariate nonparametric correlations showed significant positive relationships among β and prepregnancy diabetes (r = 0.065), maternal prepregnancy weight (r = 0.17), prepregnancy BMI (r = 0.163), average disk thickness (r = 0.47), and relative variability in disk thickness (r = 0.24) but a negative correlation with gestational age (r = –0.19). Shape abnormalities have been described in the NCPP,[33] but we tested whether our markers of irregular shape (sigma and relative symmetric difference)[53,54] were associated with diabetic features in our modern birth cohort. Sigma and the relative symmetric difference were each correlated with maternal pregnancy weight and BMI (each r ~ –0.10), but not with pregestational diabetes, first O'Sullivan, or glycemic load. The contrast of our findings with those described earlier may point to a difference in the underlying maternal disease in the 1950–1960s compared to the last decade, but confirms the contribution of maternal metabolic pathology on the early (fractal) expansion of the placenta prior to mid-gestation.

Because both gestational age and abnormal shape are associated with thinner placentas, partial correlations that adjusted for these factors were performed. Weaker but still significant associations of greater β (less efficient placenta) with maternal prepregnancy weight, prepregnancy BMI, and gestational weight gain were seen (r = 0.10, 0.098, and 0.088, respectively). The correlations of altered β with disk thickness were either unchanged (relative variability in disk thickness, r = 0.24) or stronger (average disk thickness, r = 0.49) after adjustment for gestational age shape and measures of irregular disk shape. Adjusting for these two factors plus pregestational diabetes or for gestational diabetes did not significantly affect the strength of correlations of β with either maternal or placental thickness variables. Including prepregnancy maternal BMI demonstrated persistent correlations of β with maternal weight gain in pregnancy (r = 0.12), average disk thickness (r = 0.48), and thickness variability (r = 0.24). Inclusion of maternal glycemic load and first O'Sullivan reduced the correlation of maternal factors with β but had no effect on the correlation of β with disk thickness, consistent with our prior findings that thicker placentas have reduced functional efficiency. Controlling for the gestational age, shape, diagnosis of diabetes, prepregnancy weight, first O'Sullivan and glycemic load in the model, and disk thickness and its variability remained significantly correlated with pregnancy weight gain. These observations are consistent with observations that abnormal placental morphometry of placental exchange surface in even cases of mild hyperglycemia.[55] Animal models are consistent with increased placental cell proliferation at defined developmental stages and in specific sites.[56] Although some components of diabetic metabolic pathology that impact placenta growth can be measured, weight gain in pregnancy appears to have effects that are separable, pointing to the importance of obstetrician's encouragement of healthy weight preconception and weight gain during pregnancy. Recent epigenetic studies suggest a direct effect of gestational exposure to diabetes on epigenetic modifications considered to lead to lifelong disease risks.[57]

PLACENTAL HISTOPATHOLOGY AND DIABETES

Just as there is no gross placental appearance diagnostic for diabetes or related conditions, there is no pathognomonic histology or histopathology. We have previously presented a categorization scheme that classified histopathology lesions into the following major histopathology types.

Acute Inflammation

Acute inflammation of the placenta is most commonly a reflection of maternal and/or fetal responses to the intraamniotic presence of acute inflammatory mediators such as interleukin (IL)-1, tumor necrosis factor (TNF)-α, IL-6, and IL-8 in response to the

accumulation of chemotactic gradients from the amniotic fluid space into the extra placental membranes, chorionic plate, and umbilical cord. Maternal neutrophils are recruited from the decidual maternal spiral artery vasculature, the maternal neutrophils circulating in the blood perfusing the intervillous space, and fetal neutrophils are recruited from the fetal arteries and veins of the umbilical cord and chorionic plate.

Just as diabetes is considered a risk factor for infection in the adult patient, infants of mothers with diabetes have been described to be at an increased risk for early infectious complications.[58,59] In a community hospital population, 13 of 148 (9%) consecutive infants of mothers with diabetes showed histological evidence of a fetal inflammatory response, compared to 0% from 161 consecutive clinically normal placentas.[59] The fetal inflammatory response has been suggested to be the mediator of the epidemiologic association of clinical chorionitis with long-term neurodevelopmental risk.[60] In a study of gravidas without gestational or pre-existing diabetes who had singleton pregnancies that resulted in live births, maternal plasma glucose levels at 24–28 weeks gestation were directly related to the increased risk of clinical chorioamnionitis. The authors used the sample median (99 mg/dL) for the 50 g glucose screening test as a cutoff point, with an additional stratum consisting of those women not meeting criteria for diagnosis of gestational diabetes but with glucose concentrations suggesting hyperglycemia (>130 mg/dL). Interestingly enough, this study demonstrated an interaction between clinical chorioamnionitis and the highest glucose concentrations in this nondiabetic population. The adjusted odds ratio for preterm birth at ≤32 completed weeks gestation for chorioamnionitis was 3.43 (5%–95% confidence interval [CI] 1.22–9.65) after adjusting for the effects of a wide range of confounders, including age, parity, ethnicity, cigarette smoking, BMI, gestational weight gain, and prior preterm delivery. For those gravidas with the highest stratum of glucose concentrations (>130 mg/dL) and clinical chorioamnionitis, odds of very preterm births were increased to 11.88 (5%–95% CI 2.24–62.8).[61] This epidemiological finding has a physiological basis. Studies of urinary tract infections have suggested that the increased prevalence of both asymptomatic and symptomatic bacteria in patients with diabetes may be explained by diabetes-induced abnormalities in local urinary cytokine secretion, and in altered ability of potential pathogenic organisms to adhere to the urinary epithelium.[62] Animal models suggest that diabetes prolongs the inflammatory response to bacterial stimulation. In control nondiabetic mice, the acute inflammatory infiltrate induced by inoculation with *Porphyromonas gingivalis* had subsided by day three, with lack of local cytokine gene expression. Diabetic mice, by contrast, demonstrated a persistent inflammatory infiltrate, accompanied by persistent expression at the molecular level of TNF-α and the chemokines MCP-1 and MCP-2. This persistence could be reversed by inhibition of TNF-α by Enbrel.[63] Thus, infections in diabetics may result in more protracted tissue injury due to a more prolonged inflammatory response. More protracted damage is recognized clinically in the context of delayed wound healing. In addition to cytokine dysregulation, vascular, neuropathic, and biochemical abnormalities are each likely contributors to the overall clinical impression of impaired wound healing.[64] Any infection in a diabetic pregnancy may, therefore, have a greater damage potential due to the cytokine dysregulation.

The risk of infection in diabetic pregnancy appears to vary by the etiologic agent. Increased rates of infections with *Staphylococcus aureus* have been reported.[65] There has recently been a reported 80% and 430% increased odds of vaginal mycoses in gestational diabetics and type I diabetes, respectively, compared to controls.[66] However, there is controversy regarding the potential for carbohydrate intolerance to facilitate group B streptococcus colonization during pregnancy. Ramos et al.[67] found a 2.56-fold increased risk (5%–95% CI 1.6–4.1) of colonization in diabetic women compared to nondiabetic controls. The proportion of colonized women did not vary between women with pregestational diabetes and those with gestational diabetes alone, or with white group classification.[67] However, Langer's team at the University of Texas at San Antonio[68] found no difference in colonization rates between diabetic and gestational diabetic women and perinatal morbidity associated with group B streptococcal colonization in pregnancy. It should be noted that their control and diabetic rates of colonization were each ~50% that observed in the control population reported by Ramos et al.,[67] which may account for the differences between the two studies.

Chronic Inflammation

Chronic placental inflammation is a complex diagnosis that involves the sometimes subjective identification of abnormal numbers and/or types of immune cells in one or more sites within the placenta and decidua. The most clearly defined entities include chronic villitis and chronic intervillositis, terms that denote mononuclear leukocyte invasion of chorionic villi and abnormal increase in mononuclear cells in the intervillous space, respectively. The differential diagnosis for these lesions includes both the congenital viral infection and the more poorly characterized "immune" types of pathology. The latter include both putatively autoimmune and alloimmune pathologies. The awareness of the pervasive chronic systemic inflammatory pathology seen in women with diabetes has increased with increased understanding of the pathophysiology of metabolic syndrome, a condition that commonly co-occurs with diabetes. However, elevated CRP, a marker of the chronic and persistent immune dysregulation, is found in a sizable proportion of women with gestational diabetes, in the absence of a diagnosis of metabolic syndrome.[69] It is notable that even the food choices (such as high-fat meals) that may underlie variations in maternal weight may themselves incite postprandial systemic inflammation; the data from a recent meta-analysis of 57 studies indicate that most circulating markers of inflammation, such as cytokines and soluble adhesion molecules, were not consistently elevated. However, features typical of activated leukocytes, including expression of surface markers, mRNA, and relevant proteins, were almost universally elevated, with kinetics resembling those of a response to low-dose endotoxin.[70] Chronic low-grade inflammation with and without insulin resistance may also underlie the ovarian dysfunction that presents as polycystic ovarian disease.[71] Thus, the immune dysregulation of diabetes may alter odds of conception as well as delivery of a healthy newborn.

In the same series of 148 consecutive pregnancies complicated by gestational diabetes, 23% demonstrated chronic villitis.[59] The baseline rate of chronic villitis is difficult to determine, as few investigators have occasion to study any other than those

placentas that are not discarded in the labor and delivery suite but are referred to the pathology department for examination. While these placentas often include catastrophic obstetric complications, many placentas are referred, at least in the United States, for more subtle obstetric complications such as fetal heart rate tracing abnormalities, pregnancies in which medical legal risk may be more of a motivator for investigation then immediate neonatal concerns. Knox and Fox[72] reported a rate of 13.8% in 1000 "randomly selected" placentas. One study of very preterm births (less than 32 weeks) excluded cases diagnosed with diabetes.[73] In that otherwise consecutive series, 3% of the 353 spontaneous very preterm births showed chronic villitis compared to 30% of the 76 cases of very preterm preeclampsia.[74] At term, rates of chronic villitis were 30% in growth-restricted infants and 19% in term infants whose placentas were referred to the pathology department for diagnostic examination.[73] Maternal diabetes is recognized accompanying many histologic presentations of chronic placental inflammation.[73,75] In summary, admittedly sparse data suggest that chronic villitis is more common in diabetic pregnancies, with rates approaching those seen in fetal growth restriction and extreme preterm preeclampsia.

What is the basis for an increased rate of chronic villitis in diabetes? Chronic villitis can mark a congenital viral infection, but there is no reported predisposition to viral infection in diabetes. Viral infection has been suggested as a factor that may induce diabetes, but the data are far more consistent for immunological abnormalities to exist in prediabetic[76] and diabetic[77] states. Activation of toll receptors by double-stranded RNA or poly-IC (viral mimic) through induction of interferon (IFN)-α has been proposed to activate or accelerate immune-mediated beta cell destruction. This hypothesis links the clinical evidence that IFN-α therapy is associated with autoimmune diseases, demonstrating elevated serum IFN-α levels in type 1 diabetes to the animal models that suggest, in the appropriate genetic context, the viral mimic poly-IC can induce insulinitis and/or diabetes.[78] As with other topics touched upon in this chapter, obesity alone also shows strong evidence of chronic immune dysregulation and chronic systemic inflammation.[79]

Maternal Vascular Pathology

During pregnancy, adaptive changes associated with endovascular trophoblast invasion occurring in the majority of spiral arteries lead to dramatic increases in diameter.[80] In complicated pregnancies, however, this vascular adaptation may be disturbed. When placental growth is restricted, uteroplacental vascular conversion may take place only in fewer placental bed arteries. Endovascular trophoblast conversion and modification of the maternal vascular anatomy may be restricted even in those vessels exposed to invasive trophoblast; this is classic for preterm preeclampsia. Abnormal uteroplacental vascular conversion and uteroplacental vascular damage also appears to underlie a significant proportion of spontaneous preterm births.[81–83] Placental damage secondary to chronic uteroplacental vascular malperfusion (resulting from abnormal uteroplacental conversion) may be the source of the stimulus leading to systemic endothelial cell activation in preeclampsia.[84] Despite the overall metabolic effects of growth promotion, placental damage can result in placental dysfunction restricting fetal growth.

The pathways to placental damage and potential fetal compromise are complex, with likely feed-forward or synergy in achieving the effect of maternal vascular pathology. In diabetes, insulin resistance is well appreciated to alter endothelial nitric oxide production.[85,86] Insulin resistance in diabetes and obesity may be initially due to abnormal serum lipids; free fatty acids were found to inhibit insulin-mediated glucose uptake via effects on the glucose transporter protein GLUT4.[87] As insulin resistance persists over time, other components of the metabolic syndrome develop, including increased plasma PAI-1[21] (and prothrombotic tendency) and oxidized lipoproteins.[21] However, endothelial dysfunction is an early phenomenon. In a recent study of 32 pregnancies, 9 complicated by poor first trimester glycemic control, the placental volumes at 11–13 ± 6weeks did not differ between the two groups, but the vascularization index, flow index, and the velocity flow index were significantly increased in the pregnancies with poor glycemic control (each $P < 0.004$), with the increase in each parameter increased with poor glycemic controls (as indicated by HbA1c ≥ 7).[88] Endothelial dysfunction (measured by reduced vasodilatation) is directly related to degree of hyperglycemia,[89] and even short-term hyperglycemia results in local generation of reactive oxidative species that are the agents of oxidative stress-related damage. Endothelial dysfunction is not just a result of insulin resistance and diabetes; it may itself be a cause of diabetes. As summarized by Hsueh et al.,[89] a number of interventions designed to improve endothelial function and minimize risks of cardiovascular disease also prevent diabetes. Again obesity alone has been demonstrated to induce insulin resistance secondary to inflammation generated by the adipose tissue proper.[90]

The uteroplacental arteries that undergo dramatic morphologic alteration may be particularly susceptible to the types of vascular injury that can operate in diabetes and related metabolic conditions. First, early in the conversion process, the uteroplacental arteries are devoid of endothelium. Deposition of oxidized lipids and other procoagulant serum proteins such as lipoprotein(a)[91] in the future fibrinoid wall may be a "time bomb" that may result in a thrombosis later in gestation. During the time of active vascular conversion, the fibrinoid wall is highly permeable to even mid-sized molecules such as IgG. The increase in cardiac output and the disproportionately greater increase in uterine blood flow require minimal shear stress, optimal viscosity, and minimal leukocyte and platelet activation to reduce the odds of a maternal vascular thrombosis. None of these is present in diabetes; metabolic perturbations from hyperglycemia result in disturbed endothelium-dependent relaxation, activation of coagulation pathways, depressed fibrinolysis, and other abnormalities in vascular homeostasis (see above), as well as immunologic changes that may modify vascular function.

Therefore, the evidence that uteroplacental vascular pathology complicates many diabetic pregnancies cannot come as a surprise. Of interest, however, is the consensus that the most consistent finding in histopathology studies of diabetic placentas is their inconsistency; this might be expected from a disease with variable combinations of growth-promoting and growth-restricting effects. There is some level of consensus that, as put by Mayhew and Sampson,[92] the homeostatic steady state is perturbed in the diabetic placenta. Studies that attempt to demonstrate lesion

differences based on White's classification, glycemic control, or levels of glycemia do not show consistent findings, or any correlation of lesion presence/severity, duration of diabetes, or degree of control. Lesions may be "more common in diabetes" but "not a uniform finding."[92] Foidart[93] emphasizes the multifactorial etiology of maternal uteroplacental vascular pathology by demonstrating that a wide range of factors can increase the risk of uteroplacental vascular pathology, but no single factor is sufficiently sensitive or specific to predict inevitable or even likely uteroplacental vascular pathology. Furthermore, multifactorial causality was, in their population, the rule; in most cases, uteroplacental vascular pathology risk was attributable to the combined presence of two (or more) risk factors.[93]

Fetal Vascular Pathology (Including Umbilical Cord Pathology)

The fetal vascular changes associated with diabetes and diabetic-type metabolic pathology include changes in normal vascularization of terminal villi of the delivered term placenta that have been correlated with poor glycemic control.[94,95] Abnormal villous maturation, with reduced development of the terminal villi that are essential for the normal increase in placental functional efficiency at term, is also more common in association with pregestational and gestational diabetes.[96] Computerized morphometry in a small sample also suggested that there was a very striking decreased in villous vascular volumes in pregestational diabetes despite clinically good control.[97] Jauniaux and Burton also found increased volumes of trophoblast and stroma, but not capillaries, while strictly macrosomic infants demonstrated an increase in the surface area of both villi and the fetal capillaries,[98] suggesting that the pathways of macrosomia and diabetes that lead to a large infant may be distinguished at the placental level. However, a recent small study of 17 type 1 diabetic and14 control placentas found striking variability in the diabetic placentas, with areas of increased as well as decreased villous vascularity, with increased branching of capillaries in diabetic placentas. This study concluded that "type 1 maternal diabetes enhances the surface area of the capillary wall by elongation, enlargement of diameter and higher branching of villous capillaries," suggesting that while these features "disrupt[s] the stromal structure of terminal villi,"[99] the fetal placental vascular effects of maternal diabetes and diabetic type metabolic pathology remain inconsistent and therefore incompletely understood.

Fetal placental vascular pathology may be the pathology type with the greatest risk for long-term poor neurodevelopmental outcome. Simply based on the anatomy of the fetal circulation, placental venous thrombi will preferentially embolize to the cerebral cortex, as they are shunted across the foramen ovale from the right to the left heart and, therefore, may access the carotid circulation, rather than be trapped in the pulmonary capillary bed. Fetal placental vascular pathology can be caused by placental damage by chronic villitis[100] (with inflamed villous endothelium predisposing to placental vessel thrombosis and embolism to the fetus) or maternal vascular pathology[100–102] (secondary to placental infarct or abruption). The list of case reports and small case series of fetal thrombosis and/or stroke associated with maternal diabetes is compelling.[103–108] Other series have generally focused on especially high-risk groups such as stillborns or neonatal deaths[109] or very-low-birth-weight infants[110–112]; one study of placental lesions demonstrated an association between cerebral palsy and neurological impairment following term birth.[113]

Maternal vascular pathology can affect the fetal placental vasculature without necessarily destroying placental tissue (in infarct or abruption). Abnormal maternal intervillous perfusion can deform the normal processes of villous arborization[97] and villous capillary growth,[56] induce syncytial necrosis,[57] and, via infarct, directly damage or destroy the fetal placental vasculature.[114] When there is also gross placental injury (as in infarct or abruption), diabetes may exacerbate the negative effects on fetal placental vasculature. Elevated glucose levels may, in and of themselves, induce cell death, possibly via glucose-induced TNF-α secretion.[115] Diabetic tissues, including the heart, have been shown to be more sensitive to ischemia/reperfusion injury.[116] The mechanisms by which this exaggerated tissue damage develops has been variously attributed to diabetic effects to alter neutrophil adhesion, on endothelial and myocyte dysfunction, and on tissue energetics and oxidative stress.[108,109] While preexisting sensitivity has been proposed, others have found evidence that suggest circulating elements in the bloodstream are the critical conditioning factors that result in this excessive vulnerability.[117–119]

Fetal vascular damage can also be caused by fetal vascular dysfunction; there is also evidence that the diabetic environment can alter fetal vascular homeostasis. In the fetal sheep, hyperinsulinemia resulted in a significant decrease in protein C, and relative increases in fibrinogen factors V, VII, and XI when the insulin-treated group was compared with the controls.[120] These changes are consistent with the perturbations of homeostasis observed in adult humans.[121] As mentioned, a single umbilical artery is more common in infants of diabetic mothers.[39] Even in less severe forms of impaired glucose metabolism, disturbances in platelet activation have been found to significantly affect both biochemical and morphological vessel walls and tissue functions in the umbilicoplacental unit.[122–124] Adenosine transport is also increased in the umbilical vascular media in diabetes, possibly also associated with altered nitric oxide homeostasis. Once a clot has formed, its time course to resorption is also altered. Nappi et al.[122] placed endothelial cells from the umbilical veins of infants of mothers without diabetes in culture and added thrombin to cell-free plasma. The resultant clots retracted more quickly than those induced in umbilical vein endothelia from mothers without diabetes. The early retraction of fibrin clots would result in the exposure of subendothelial layers to the circulation, predisposing to recurrent thrombosis. The infant of a diabetic mother is at risk for polycythemia and increased blood viscosity.[123] Hyperviscosity increases shear stress at branch points in the vascular tree; shear stress modulates vascular medial and endothelial gene expression[124] and contributes to the overall vascular fragility of the infant of the mother with diabetes. Finally, prostacyclin production is reduced in these infants, laying yet another potential straw on the back of the fetal vasculature.[125]

The effects of maternal diabetes on the fetal placental vasculature are more than hypothetical. While reactive oxygen species may contribute to normal placental development,[126] Lyall et al.[127] demonstrated that more intense nitrotyrosine staining was apparent in vascular endothelium and villous stroma (both $P < 0.02$) of diabetic placentas. Peroxynitrite is a strong biological oxidizing

agent that reacts with DNA, membrane phospholipids, sulfhydryl groups, and tyrosine. Nitrotyrosine deposition in the fetal placental vasculature thus implies the local presence of oxidative stress. Excess superoxide dismutase activity and protein carbonyl (a key antioxidant) content have been identified in placentas obtained from diabetic women compared to controls, suggesting that there are normal placental vascular defenses against oxidative stress–induced vascular injury. Both vascular medial and endothelial cell function may be altered in the fetus of a diabetic mother. Oxidative stress peaks by the second trimester of pregnancy; thus, the pathophysiology of diabetes and related metabolic conditions may be particularly problematic to the fetus at a time of rapid growth and visceral maturation.[128–130]

As important as gestational complications are, it must be noted that maternal gestational diabetes must be considered an important flag for lifelong risk of vascular disease.[131,132] The close association of oxidative stress and inflammation[133] makes diabetes especially in the insulin-resistant context of pregnancy a "double whammy," exacerbated by a reduced ability to heal the cellular wounds inflicted by these processes.[134] Change of lifelong habits that may predispose to gestational or pregestational diabetes can be difficult to accomplish, but this complication of pregnancy can impact the likelihood of a mother seeing her grandchildren.

SUMMARY

There is no single gross of histologic pathology that is diagnostic of maternal diabetes, or even of the diabetes-associated metabolic pathologies in general. However, placental gross and histologic pathology can combine to document aspects of an altered intrauterine environment that may modify placental and fetal growth trajectories, and stress placental and fetal homeostasis. Thoughtful gross and histologic examination of the placenta in diabetes and diabetes-related metabolic states such as obesity may contribute to understanding at which time(s) in pregnancy effects of excessive growth promotion and inflammatory and oxidative stress related, singly or jointly, alter the normal physiology of the fetus and placenta.

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Metabolic and Hormonal Changes in Normal and Diabetic Pregnancy

6

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Science, like life, feeds on its own decay. New facts burst old rules; then newly divined conceptions bind an old and new together into a reconciling law.

—William James

Key Points

- Hormonal changes in pregnancy result in changes in glucose tolerance that resemble a "diabetogenic state."
- Maternal insulin resistance is associated with increased adipose tissue early in gestation and nutrient availability in late gestation.
- The hyperinsulinemia of pregnancy is mainly the result of pancreatic β-cell compensation for physiologic insulin resistance.
- Postreceptor defects in insulin signaling may contribute to the pathogenesis of gestational diabetes mellitus and the increased risk for type 2 diabetes later in life.
- Placental and maternal adipose tissue hormones are associated with increased insulin resistance and directly related to the increase in placental growth and endocrine function.
- Nutrients and essential trace elements are associated with insulin resistance in normal and diabetic pregnancies.

INTRODUCTION

This chapter will address the development of insulin resistance during pregnancy; the role of hormones and other factors associated with insulin resistance and secretion; the insulin-signaling system during normal and diabetic pregnancy; and the metabolic predictors of diabetes. Glucose homeostasis and the development of insulin resistance in normal pregnancy as well as in pregnancies complicated by gestational diabetes mellitus (GDM) are discussed in detail in Chapter 12.

DEVELOPMENT OF INSULIN RESISTANCE DURING PREGNANCY

Normal pregnancy has been characterized as a "diabetogenic state" due to the change in the pattern of secretion of insulin, resulting in increased postprandial glucose and insulin response to this increase in late pregnancy. Therefore, pregnancy is a progressive condition in which increasing insulin resistance leads to an increase in insulin secretion. The association between increased insulin resistance and the resulting increase in insulin secretion (hyperinsulinemia) is met in the majority of pregnant women; otherwise, abnormal glucose tolerance develops. After delivery, the diabetogenic state of pregnancy resolves.[1,2] Some have reported that women who developed GDM were more insulin resistant than women without GDM.[1,3,4] In addition, it has been suggested that due to the high level of estrogen early in pregnancy, there is an increased insulin sensitivity in both normal and GDM pregnancies.[5]

Glucose is transferred through the placenta by facilitated diffusion, and as mentioned earlier, the changes in the patterns of insulin secretion cause postprandial hyperglycemia. In turn, the postprandial elevation will increase nutrient availability (glucose) to the fetus. In addition, peripheral insulin resistance is more pronounced in the skeletal muscle than in the adipose tissue, resulting in ingested nutrients being shunted toward the adipose tissue. This promotes maternal anabolism and energy storage needed in late pregnancy when fetal growth is maximal.

ASSESSMENT OF INSULIN RESISTANCE

As early as in 1956, Burt[6] demonstrated that pregnant women experience fewer hypoglycemic events in response to insulin infusion than nongravid women. Since then, several mathematical and physiological models have been developed to assess insulin resistance and sensitivity, including the hyperinsulinemic-euglycemic clamp, the Bergman model, IS-QUICKI index (quantitative insulin sensitivity check index), and IS-HOMA index (homeostasis model assessment of insulin resistance). The minimal Bergman model and the

hyperinsulinemic-euglycemic clamp[7,8] have become the premier standard techniques for studying secretion, resistance, and sensitivity relationships during the pregnant and nonpregnant states. It has been demonstrated that insulin sensitivity derived from an oral glucose tolerance test (IS-OGTT) or fasting glucose/insulin levels (IS-QUICKI or IS-HOMA) is comparable with that derived from the clamp, and that all methods can be used to predict insulin sensitivity in women before and during pregnancy. Yet, although univariate analysis yielded significant correlation between the clamp results and IS-QUICKI, IS-HOMA, and IS-OGTT, multivariate analysis taking into account normal glucose tolerant (NGT) women versus GDM patients demonstrated that the IS-OGTT is the superior method of all three.[9] The use of the oral glucose tolerance test (OGTT), Bergman model, IS-QUICKI, or IS-HOMA for studying insulin sensitivity is easier to perform, less costly, and may serve as a rapid screening test even in clinical settings, while the hyperinsulinemic-euglycemic clamp is more labor intensive and costlier but provides the ultimate standard for this investigation.

Recently, it has been shown that maternal serum levels of glucose and C-peptide taken at fasting and 1 hour after 75 g of oral glucose can also be used to assess insulin sensitivity with strong correlation to the methods mentioned earlier.[10] In addition, IS-HOMA has been studied in a clinical setting and was found to corroborate with severity of GDM and obstetrical outcomes.[11,12]

OBESITY, INSULIN RESISTANCE, AND GLUCOSE PROFILE

Catalano et al.,[13,14] using the hyperinsulinemic-euglycemic clamp model, reported 60% increase in the first-phase insulin response to intravenous glucose infusion and a 130% increase in the second phase among obese women with normal glucose tolerance test with advancing gestation, compared with 200%–250% increase among their lean counterparts. He speculated that relative β-cell dysfunction due to chronic decrease in insulin sensitivity was partially responsible for this phenomenon. In the same study, it was demonstrated that obese women with GDM had significantly greater second-phase insulin response, but not first-phase response, compared with obese women without GDM. In addition, obese women with GDM had lower insulin sensitivity and experienced less suppression of endogenous glucose production in response to insulin infusion, with respect to obese women without GDM. Some of these finding were also supported by an earlier study of obese non-GDM patients, which demonstrated a reduction in the endogenous suppression of hepatic glucose production, thereby indicating a further decrease in hepatic insulin sensitivity.[15] The relationship between decreased maternal insulin sensitivity and fetal overgrowth particularly in obese women and women with GDM may help explain the increased incidence of adolescent obesity and related glucose intolerance in the offspring of these women.

Due to the diverse characteristics of obese and nonobese patients, we investigated the ambulatory daily glycemic profile in the second half of pregnancy in obese and nonobese, nondiabetic women using continuous glucose monitoring.[16] Obese subjects were characterized by higher postprandial glucose peak values, increased one- and two-hour postprandial glucose levels, and increased time interval for glucose peak in comparison with nonobese subjects. Moreover, obese subjects had significantly lower mean blood glucose levels during the night (23:00 pm to 06:00 am) in comparison with nonobese subjects.

PANCREATIC β-CELL FUNCTION AND INSULIN SIGNALING SYSTEM

Most commonly, assessment of β-cell function is performed by measuring fasting insulin concentration or as a response to glucose infusion. The cellular determinants of insulin resistance are still not fully understood. During pregnancy, fasting plasma insulin increases gradually; these levels are twofold higher in the third trimester than before pregnancy. Women whose pregnancies are compromised by GDM have fasting insulin levels equal to or higher than those of nondiabetic pregnant women, with the highest levels among obese women with GDM. Oral and intravenous glucose tolerance deteriorates only slightly despite the reduction in insulin sensitivity during normal pregnancy.[2] A gradual increase in insulin secretion by the β-cells is the prime apparatus responsible for this phenomenon. Kuhl[17] and Bergman et al.[18] reported an exaggerated relationship between insulin sensitivity and β-cell responsiveness to glucose in both pregnant and nonpregnant women, which indicatethat β-cell dysfunction plays a role in pathological states such as GDM and signify the magnitude of the change in insulin secretion that is necessary to maintain glucose tolerance. The flexibility of β-cell function allows the maintenance of normal circulating glucose levels despite wide deviations in insulin action. In pregnant and nonpregnant women, a comparable association between β-cell function and insulin secretion has been noted.[2,19] These findings further corroborate the hypothesis that the hyperinsulinemia of pregnancy is largely the result of pancreatic β-cell compensation for physiologic insulin resistance. The ability of β-cells to maintain normal capacity of insulin secretion in response to increased insulin resistance is associated with only slight deterioration in glucose tolerance late in pregnancy.[20]

Other studies have validated the contribution of the β-cell inability to compensate the rising insulin resistance to the development of GDM. Catalano et al.[21] prospectively and longitudinally followed up 16 patients from 12 weeks of gestation onward and found that regardless of glucose tolerance, as pregnancy progressed, the efficacy of infused insulin decreased basal C-peptide concentrations (surrogate for β-cell function) in clamp studies. Saisho et al.[22] in their prospective study using insulin-resistance mathematical models found that β-cell function deteriorates as pregnancy advances, and more so among glucose intolerant parturients than in NGT parturients. They later compared a larger cohort of women with GDM with NGT women and found that the disposition index (a surrogate marker for β-cell function) correlated with the severity of GDM and with the total insulin dosage needed to achieve glycemic control.[23]

The insulin receptor is part of the growth factor receptor family that possesses an intrinsic tyrosine kinase activity.[24] Insulin binding to surface receptors of circulating RBC has generally been reported to be normal in pregnant women.[25,26] Others have reported a decline in binding of insulin to adipocytes in pregnant versus nonpregnant women.[27,28] Most notably, binding of insulin

to the skeletal muscle, the target tissue that mainly contributes to the total body insulin resistance, has been reported to be similar in pregnant and nonpregnant states.[29] This finding supports the assumption that insulin resistance is mainly a postreceptor defect.

EVIDENCE FOR POSTRECEPTOR DEFECT IN INSULIN SIGNALING

A family of membrane proteins, GLUT1 to GLUT4, which have a significant sequence likeness, is responsible for glucose uptake by cells. GLUT4 is the main insulin-sensitive glucose transport whose action is required in the skeletal and cardiac muscles and adipose tissue. Garvey et al.[30] were the first to demonstrate that there were no significant differences in the glucose transport (GLUT4) responsible for insulin action in the skeletal muscles in pregnant GDM, pregnant NGT, and nonpregnant women, although they did find that in GDM pregnant women, binding capacity to the receptor was diminished. Later, it was reported that the insulin-stimulated glucose transport in adipose tissue was reduced by 60% at term in women with GDM compared to nondiabetic pregnant women, and that at 50% of patients with GDM, GLUT4 content in adipocytes was profoundly depleted.[31] Additional factors such as cytokine tumor necrosis factor have been cited as a potential influence on insulin receptor substrate function in the signaling cascade.[24]

PROTEIN METABOLISM

In addition to glucose, protein is essential for fetal growth. Nitrogen retention is increased during pregnancy, in both maternal and fetal compartments. It is estimated that there is a 500-g increase in protein accumulation by about week 30. A significant decrease occurs in most fasting concentrations of maternal amino acid in early pregnancy, before the accumulation of significant maternal or fetal tissue.[32] The impending changes in fasting amino acid metabolism occur after a shorter period of fasting in contrast to nonpregnant women. This occurrence may be another manifestation of the accelerated starvation in pregnancy. Duggleby and Jackson[33] reported that during pregnancy, protein synthesis in the first trimester is similar to that of nonpregnant women, increased by 15% during the second trimester and by further 25% in the third trimester. Amino acids can be used for either protein accretion or oxidized as an energy source. In general, there is a modest shift in oxidation in early pregnancy with an accretion of amino acids for protein synthesis in late gestation.[33] Kalhan et al. have suggested that there are significant pregnancy-related changes in maternal protein metabolism early in gestation before any significant increase in fetal protein accumulation.[34] There is paucity of data on the effects of insulin infusion on amino acid turnover during pregnancy in women with and without GDM. It appears that there may be a slight decrease in the rate of protein breakdown during fasting[35] and a slight increase in protein turnover during the day.[36]

Zimmer et al.[37] aimed to assess protein metabolism in untreated GDM patients compared with NGT patients in the third trimester. They reported that although hepatic glucose release and whole body proteolysis were not different between the groups, fasting insulin levels needed to maintain homeostasis were three- to fivefold higher among GDM patients. Butte et al.[38] later reported that in insulin-treated GDM parturients, protein turnover was normalized, while the concentration of amino acids was elevated both antepartum and 6 weeks postpartum, despite good glycemic control.

LIPID METABOLISM

Darmady and Postle measured serum cholesterol and triacylglycerol before, during, and after pregnancy in nondiabetic women and found that cholesterol and triacylglycerol decreased at about 7 weeks of gestation and increased progressively thereafter until term.[39] In the fed state, the release of free fatty acids (FFAs) from adipose tissue is suppressed by the antilipolytic actions of insulin so that FFA levels are only slightly higher in pregnancy during the first hours postprandial. On the other hand, the stimulation of lipolysis in pregnancy causes an increase in circulating FFA when insulin levels decrease. Therefore, fasting and postprandial FFA levels are augmented in pregnancy in comparison to the nonpregnant state.[40] Increases in maternal FFA in late gestation have been purported to be related to the decrease in maternal glucose insulin sensitivity in late pregnancy. FFA have also been associated with fetal overgrowth, especially of adipose tissue. It has also been hypothesized that neonatal birth weight is positively correlated with triacylglycerol and FFA concentrations.[41] Infants of obese women were reported to have not only increased birth weight and skin fold measurements but increased serum FFAs compared with infants of lean women.[42] In GDM, especially during the third trimester, there has been a reported associated increase in triacylglycerol and decrease in high-density lipoprotein concentration.[43] Montelongo et al.[44] reported little change in FFA concentrations throughout pregnancy. It has also been demonstrated that GDM women have an increase in total triacylglycerol but lower low-density lipoprotein cholesterol.[45] Studies in nondiabetic pregnant and GDM women[46,47] using the hyperinsulinemic-euglycemic clamp showed a decreased ability of insulin to suppress FFA with advancing gestation in both groups. This ability of insulin to suppress plasma FFA was significantly lower in women with GDM.[47] These studies demonstrate that insulin resistance to nutrients decreases in all women with advancing gestation.

Pappa et al. reported that in diet-controlled GDM, ketogenic amino acids are released in slow rates from skeletal muscle and are catabolized mainly in the liver, in contrast to NGT pregnancies in which fatty acids are catabolized in both the liver and the peripheral tissues.[48] Chen et al. assessed the circulating FFA and fatty acid intake among GDM patients, patients with abnormal glucose challenge test (GCT) but normal OGTT (termed by them hyperglycemia less severe than GDM), and NGT controls. They found that there was a graded increase among groups in total FFA in the third trimester and that the increase correlated with body mass index (BMI).[49]

Adipocyte fatty acid–binding protein (AFABP) is an adipokine whose serum levels correlate with the development of metabolic syndrome and cardiovascular disease. In a study among GDM patients in comparison with NGT controls, it was found that AFABP levels were significantly higher in GDM patients (22.9 μg/L vs. 18.3 μg/L, $P < 0.05$) and those markers of adiposity such as BMI, leptin, triglycerides, and serum creatinine were also

independently associated with ADABP levels.[50] In another report, AFABP levels in maternal serum were higher in GDM patients compared with NGT controls, whereas they were found to be lower in cord blood. In addition, AFABP levels were higher in cord blood than in maternal serum. The conclusion of this study was that fetal tissues are the main source of AFABP, and that in GDM patients, the fetus AFABP values correlate with adiposity markers.[51]

HORMONAL EFFECT IN NORMAL AND DIABETIC PREGNANCY

The physiological changes responsible for insulin resistance in pregnancy appear to be related to the metabolic effects of several hormones and other factors that are elevated in the maternal circulation. Evidence to support the impact of these hormones on insulin resistance is related to the fact that development of insulin resistance during pregnancy tends to parallel the growth of the fetomaternal unit and the levels of hormones secreted by the placenta.

Estrogen and Progesterone

Early in pregnancy, progesterone and estrogen levels increase but their effect on insulin activity are offset, that is, progesterone causes insulin resistance while estrogen is protective.[52] It has been reported that progesterone accelerates the development of diabetes in female db/db mice. In contrast, RU486, an antagonist of the progesterone receptor, reduces blood glucose levels. Furthermore, after obstruction of the progesterone receptor, pancreatic islets appeared larger and secreted more insulin as a result of an increase in β-cell mass due to an increase in β-cell production.[53] Progesterone signaling may play a vital role in insulin release and pancreatic function and may affect susceptibility to diabetes. An intravenous glucose tolerance test given to estrogen-treated rats showed a significant decrease in glucose concentrations and a twofold increase in insulin concentration.[54] With the addition of progesterone, there was a 70% increase in the insulin response to the glucose challenge test; no alterations in glucose tolerance were observed.[55] In cultured rat adipocyte tissue treated with estrogen, there was no effect on glucose transport, but maximum insulin binding was increased. Progesterone was noted to decrease maximum glucose transport and insulin binding.[54,55]

A more recent report examined the expression profile of estrogen receptors (among other potential genes responsible for insulin resistance) in subcutaneous adipose tissue, visceral adipose tissue, and placenta of GDM parturients. The expression of estrogen receptor alpha and beta genes was significantly reduced in subcutaneous adipose tissue of GDM patients compared with controls, which may play a role in the pathogenesis of GDM.[56]

To simulate the plasma levels in normal pregnancy, ovariectomized rats were treated with different doses of progesterone and/or 17 β-estradiol; steroid hormones lead to the decreased insulin sensitivity. The increased insulin sensitivity during early pregnancy, when plasma concentrations of 17 β-estradiol and progesterone are low, may be the result of 17 β-estradiol.[57] Conversely, during late pregnancy, when plasma concentrations of 17 β-estradiol and progesterone are elevated, 17 β-estradiol may impede the effect of progesterone, diminishing insulin sensitivity. Therefore, the data suggest that progesterone prohibits normal adaptation of the pancreatic β-cell reserve during pregnancy and is a major contributor to increased insulin resistance.

Human Placental Lactogen

Human placental lactogen (hPL) levels increase at the onset of the second trimester causing a decrease in phosphorylation of insulin receptor substrate-1 and intense insulin resistance.[52] Overnight infusion of hPL results in abnormal glucose tolerance and enhanced insulin and glucose concentration in response to the oral glucose challenge.[58] In islet cell culture, hPL directly stimulates insulin secretion.[59] This may indicate that hPL directly regulates islet cell function and is the prime hormone responsible for enhanced islet function observed during normal pregnancy. Maternal plasma concentration of hPL increases steadily until about 34–36 weeks of gestation and is approximately proportional to placental mass. Thus, with increasing insulin, resistance is enhanced. Moreover, the levels of placental mRNA coding for hPL were found to be higher in GDM patients in comparison with nondiabetic women.[60]

Prolactin

During pregnancy, maternal prolactin levels increase 7- to 10-fold. It has been reported that the basal insulin concentration and postchallenge glucose and insulin response were greater in women with hyperprolactinemia than in healthy control subjects.[61] Corroborating studies showed that the culture of pancreatic islet cells with prolactin induces increased insulin secretion.[62] The relationship between the deterioration in glucose tolerance and plasma prolactin levels was assessed in patients with normal and diabetic pregnancies that reported no difference in basal prolactin concentrations between the two groups at either time point.[63] The prolactin levels were also not altered during the OGTTs; and there was no correlation between the deterioration in glucose tolerance and the prolactin concentrations in either group. These data suggest that abnormal prolactin levels may not be a part of the pathophysiology cascade in the development of insulin resistance and GDM. Moreover, amniotic fluid prolactin concentrations were found to be alike in GDM and non-GDM patients.[64]

Nonetheless, a recent report discovered a significant association between two minor alleles single-nucleotide polymorphism (SNP) in the prolactin receptor gene and the development of GDM, with an increased risk of 2.4-fold among those carrying the SNPs. More research is needed to rule out any potential role of prolactin in the pathogenesis of GDM.[65]

Cortisol

There is a continuous increase in cortisol levels throughout pregnancy, with concentration up to threefold at the end of pregnancy compared with nonpregnant state. One study demonstrated that under infusion of high amounts of cortisol, hepatic glucose production increased and insulin sensitivity decreased.[66] An excess of glucocorticoid in a skeletal muscle model was characterized by decreased total tyrosine phosphorylation of the insulin receptor. It is plausible to assume that glucocorticoid-induced insulin resistance is another proof for the postreceptor defect mechanism. When pregnant women with GDM were compared to pregnant women with normal glucose tolerance, the GDM subjects were found to have significantly higher levels of serum cortisol than the

control group.[67] These findings may provide the foundation for the role of cortisol in the deterioration of blood glucose tolerance in pregnancy.

Leptin

Leptin is a 16-kDa protein encoded by the *ob/ob* (obesity) gene secreted by adipocyte tissue and also produced by a number of other tissues including the stomach, intestine, and the placenta in humans. It acts on hypothalamic receptors to decrease food intake and increase energy expenditure. Fasting insulin and leptin concentrations closely correlate with body fat, making leptin a good marker of obesity and insulin resistance. Since receptors to leptin are found in the skeletal muscle, liver, pancreas, adipocyte tissue, uterus, and placenta, it may be responsible for peripheral and central insulin resistance. Reductions in leptin concentrations are caused by weight loss, fasting, and starvation; leptin concentrations are increased with weight gain and hyperinsulinemia. Using the hyperinsulinemic-euglycemic clamp studies in animal models, infusion of leptin was reported to increase the glucose utilization rate, which translates to increased insulin sensitivity.[68] Leptin levels are significantly higher in pregnancy than in the nonpregnant state, especially during the second and third trimesters, and this change in circulating leptin concentrations is generally consistent with changes in maternal fat stores and glucose metabolism.[69–71] Results of studies by Laivuori et al. suggest that pregnancy-associated increases in maternal plasma leptin may result from an upregulation of adipocyte leptin synthesis in the presence of increasing insulin resistance and hyperinsulinemia in the latter half of pregnancy.[72] Investigators have also shown that leptin directly affects whole body insulin sensitivity by regulating the efficiency of insulin-mediated glucose metabolism by skeletal muscle[73] and hepatic regulation of gluconeogenesis.[74] Leptin may also wield an acute inhibitory effect on insulin secretion.[75]

Leptin Animal Models

Leptin deficiency in ob/ob mice and leptin resistance (db/db mice with a defective leptin receptor) result in hyperphagia and decreased energy expenditure. As a result, the affected animals become obese and develop insulin resistance.[76] Moreover, an alteration in leptin action may affect GDM and fetal overgrowth.[77] Pregnant mice treated with leptin had noticeably lower glucose levels than controls during glucose and insulin challenge tests. However, despite the reduced energy intake and improved glucose tolerance, fetal overgrowth was not lowered. These results may provide confirmation that leptin administration during late gestation can decrease adiposity and enhance glucose tolerance in spontaneous GDM. Alterations in placental leptin levels may contribute to the regulation of fetal growth independently of maternal glucose levels.

Leptin in Humans

Research results in whether leptin is a diabetogenic or antidiabetogenic hormone have produced conflicting statements. Data from a large epidemiological study demonstrated that plasma leptin concentrations were positively associated with insulin resistance in men and nonpregnant women.[78] Investigators have also observed that chronic hyperglycemia is associated with a reduction in leptin concentration in the peripheral circulation.[79] Data suggest a complex relation between leptin and glucose homeostasis in humans. Kautzky-Willer et al.[80] measured plasma concentrations of leptin and β-cell hormones during fasting and after an oral glucose load (OGTT of 75 g) in GDM women and pregnant NGT women at 28 weeks gestation and compared them with nonpregnant women. Plasma leptin was higher in the GDM women than in NGT women, and higher in both these groups than in the nonpregnant controls. No change in plasma leptin concentration was induced by OGTT in any group. Basal insulin release was higher in GDM women than in the NGT women. The authors suggested that women with GDM and no change in plasma leptin on oral glucose loading have increased plasma leptin concentrations during and after pregnancy. Leptin levels and the relationship between leptin substance and insulin were assessed in pregnant GDM women.[81] There was a correlation of plasma leptin levels with fasting plasma insulin levels and plasma glucose levels measured 1 hour after oral administration of 50 g of glucose. The serum leptin levels in GDM women were significantly higher than in the women whose pregnancies were not compromised by GDM. The GDM group also showed a significant, positive correlation of serum leptin levels with glycosylated hemoglobin levels, fasting serum insulin levels, and plasma glucose levels measured 1 hour after administration of 50 g of glucose.

Leptin levels are elevated in GDM women, and leptin metabolism depends on insulin levels and the severity of the diabetes. It has been suggested that umbilical cord leptin concentration may be an independent risk factor for fetal macrosomia in nondiabetic pregnant women.[82]

Later reports further established association between leptin levels and GDM. In 2007, Maghbooli et al.[83] reported that increased leptin concentrations correlated with insulin levels, BMI, and HOMA index, and that after adjusting for possible confounders, GDM was independently associated with leptin levels. They concluded that leptin concentration ≥20ng/mL may assist in the prediction of GDM. Qiu et al.[84] reported that hyperleptinemia up to 16 weeks of gestation may predict higher risk of GDM later in pregnancy, independent of maternal adiposity. Nevertheless, other reports have failed to establish this association, but their sample sizes were considerably smaller.[85,86]

In light of the accumulated data, leptin appears to provide a key role in mediating glucose metabolism in pregnancy. Measurement of leptin alone, or combined with the assessment of other risk factors, may help identify women at high risk for developing GDM.

Adiponectin

Adiponectin is an adipose tissue hormone, which is a specific plasma protein that is secreted by adipocytes. It may facilitate the regulation of the glucose and lipid metabolism. Adiponectin decreases the hepatic glucose production and insulin resistance by up-regulating fatty acid oxidation.[87] Adiponectin also suppresses the secretion of tumor necrosis factor-α by adipose tissue, a factor that is known to contribute to insulin resistance.[88] Studies have shown that adiponectin serum levels were decreased in obese subjects[89] and patients with type 2 diabetes.[90] In studies with rhesus monkeys, adiponectin plasma levels were significantly decreased with the progression of obesity and insulin resistance.[91] In all probability, adiponectin increases insulin sensitivity by enhancing the β-oxidation of FFAs and by decreasing the intracellular concentrations of triglycerides.[92,93]

In patients with type 2 diabetes, who share the same risk factors for GDM (i.e., obesity, maternal age, ethnic origin, family history, etc.), lower serum levels of adiponectin were detected. In mice, intravenous administration of adiponectin was associated with loss of weight and reduced plasma concentrations of fatty acids[94]; the proportion of total body fat mass correlated negatively with adiponectin serum levels.[95] The data suggest that low plasma adiponectin concentration during even early pregnancy may be associated with subsequent development of GDM,[96–98] and recent reports support this theory. Lacroix et al.[99] collected blood samples from 445 women at the first and second trimesters during pregnancy. Overall, 38 women developed GDM. Compared with NGT women, GDM patients has lower adiponectin levels (9.67 μg/mL vs. 11.92 μg/mL), and the odds ratio (OR) for developing GDM was 1.12 per 1 μg/mL decrease in adiponectin ($P = 0.02$). Ferreira et al.[100] also performed a prediction analysis, by measuring serum levels of both adiponectin and visfatin at 11–13 weeks gestation. They reported that the combination of high visfatin and low adiponectin produced a prediction rate of 68% at a false positive rate of 10%. Hedderson et al.[101] examined whether prepregnancy adiponectin levels may assist in the prediction of GDM. They found that when comparing quartiles of adiponectin levels, the risk of developing GDM increases with decreasing quartile (OR 1.5 [95% confidence interval [CI] 0.7–2.9], OR 3.7 [95% CI 1.9–7.2], and OR 5.2 [95% CI 2.6–10.1], respectively, $P < 0.001$). They also observed that the combination of low adiponectin level and overweight produces ad sevenfold increase in GDM risk compared with women with normal weight and above the median adiponectin level.

At the molecular biology level, a recent study evaluated the association between adiponectin gene SNP and GDM. It was found that the SNP45TG in adiponectin gene is associated with the development of GDM,[102] and Beltcheva et al.[103] discovered a significant association between the rs266729 SNP and GDM.

Levels of adiponectin have been assessed in fetal cord at delivery.[104] Cord blood adiponectin levels were extremely high in comparison with serum levels in children and adults and were positively correlated to fetal birth weights. No correlation was found between cord adiponectin levels and maternal BMI, cord leptin, or insulin levels. Cord adiponectin levels were significantly higher compared with maternal levels at birth, and no correlation was found between cord and maternal adiponectin levels. There were no significant differences between adiponectin levels at birth and four days postpartum. These findings indicate that adiponectin in cord blood is derived from fetal and not from placental or maternal tissues. The high adiponectin levels in newborns compared with adults may be the result of deficient negative feedback on adiponectin production stemming from lack of adipocyte hypertrophy, low percentage of body fat, or a different distribution of fat storage in newborns. Adiponectin may emerge as a significant factor in carbohydrate–fat metabolism and in the development of insulin resistance during pregnancy. Data suggest that there are decreased adiponectin levels in women with GDM compared with healthy control subjects. This finding supports the concept of a common pathogenesis between type 2 diabetes and GDM. Although adiponectin level appears to rise throughout pregnancy, its contribution to gestation remains unclear.

NUTRIENTS AND ESSENTIAL TRACE ELEMENTS: THE ASSOCIATION TO INSULIN RESISTANCE IN NORMAL AND DIABETIC PREGNANCY

The metabolism of zinc, magnesium, and chromium may be altered in women with GDM. Increases in urinary excretion and lower circulating levels of these nutrients have been reported in diabetic women.

Zinc

Animal studies of zinc depletion show that zinc is required for normal glucose metabolism. A correlation has been shown between zinc and the degree of glycosuria and serum hemoglobin A_1c concentrations.[105] Serum zinc concentrations may have an insulin-like effect on glucose transport into adipocytes. Zinc enables insulin-induced glucose transport into cells by influencing the insulin signaling pathway. Therefore, zinc deficiency may explain why glucose utilization is reduced and lipolysis is enhanced. Zinc depletion also alters glucose metabolism in humans. In a study of zinc depletion in men, the results showed a rise in plasma glucose concentrations.[106] Since pregnancy is associated with increased insulin resistance, a marginal maternal zinc ingestion may be a risk factor for developing GDM. Diabetes per se also appears to alter zinc metabolism. Urinary zinc excretion is elevated in diabetic patients compared with control subjects,[107,108] and this increase may be explained with urinary protein losses. Failure to maintain established levels of glycemic control may also be related to a decrease in serum zinc levels.[109] The role of zinc in GDM has not been ascertained. Zinc transport to the fetus in diabetic rats is reduced because of either a decrease in placental transport or altered maternal or fetal zinc-binding ligands.[110] In humans, no differences in serum zinc were observed between insulin-dependent diabetic women maintaining established levels of glycemic control and pregnant control subjects.[111] Additional research is needed to establish the effects of marginal zinc status on glucose homeostasis in women during pregnancy.

Magnesium

The reduction in serum magnesium during pregnancy in both healthy and diabetic women may, in part, be due to the decline in serum albumin concentrations. Magnesium depends on insulin for the transport process into cells. Intensive insulin treatment during pregnancy in women with GDM may lead to a further decline in circulating magnesium. There are no data on the functional consequences of this lower level of magnesium during gestation in diabetic women. However, decreased levels of magnesium are associated with increased urinary loss of magnesium[112] in type 1 diabetes in comparison with controls. Serum magnesium concentrations are inversely related to glycosylated hemoglobin concentrations and glucosuria. The increased urinary losses may be related to hyperfiltration in combination with impaired tubular reabsorption. Lower levels of striated muscle magnesium were measured in patients with diabetes requiring insulin.[112] Decreases in serum magnesium and increased urinary losses of magnesium were reported in GDM women; these lower levels persisted after good glycemic control was achieved.[111]

Chromium

Chromium has been identified as an essential nutrient because it restores glucose tolerance in rats fed diets low in chromium.[113] Although rat studies may indicate that chromium facilitates insulin function, that role has not yet been specified; it is also unclear whether chromium affects pathogenesis of diabetes in humans. To test the effect of chromium supplementation on glucose tolerance in pregnancy, subjects given supplemental chromium had lower fasting and peak blood glucose levels.[113] However, the added chromium did not lower blood glucose concentrations in women with severe glucose intolerance enough to eliminate the need to receive insulin. Recent report showed that GDM patients has lower concentrations of chromium compared with NGT controls, but this observation was not significant after adjusting for parity.[114]

Vitamin D

Vitamin D was studied with relation to GDM. Wang et al.[115] investigated vitamin D deficiency among 400 Chinese women (half of which with GDM) and found that rates of serum 25-hydroxy vitamin D (25OHD) deficiency were significantly higher among GDM patients. They reported that patients with 25OHD levels <25 nmol/L has 1.8-fold risk for developing GDM. Their findings were later reproduced when it was reported that lower 25OHD levels correlated with higher HOMA-IS indices.[116] Perez-Ferre et al.[117] prospectively followed up 266 women and found 25OHD deficiency (<20 nmol/L) among 59% of them. There was inverse correlation between 25OHD levels and HOMA-IS, glycosylated hemoglobin A1c, serum insulin glucose levels at fasting and 1 hour after OGTT. Soheilykhah et al.[118] assessed vitamin D supplementation on insulin resistance in a randomized clinical trial of 120 participants starting 12 weeks of gestation. One group received 200 IU of vitamin D per day, another groups 50,000 IU per month, and the third group 50,000 IU twice a month. Insulin resistance was measured using HOMA-IS. They found that vitamin D supplementation of 50,000 IU twice a months improved insulin resistance significantly.

SUMMARY

During pregnancy, there are significant alterations in maternal metabolism that provide for the metabolic demands of the developing fetus. The development of insulin resistance in late gestation is a process common to all human pregnancies. The development of maternal insulin resistance is associated with an increase in maternal adipose tissue in early pregnancy and increased fetoplacental nutrient availability in late gestation, when 70% of fetal growth occurs. In women who develop GDM, insulin resistance is increased before conception, often in association with maternal obesity and increased risk of fetal macrosomia or overgrowth. The macrosomic infants of these women have an increased risk for the development of adolescent obesity and type 2 diabetes. GDM is also a predictor or even an early manifestation of the metabolic (insulin resistance) syndrome.

During the second trimester, there is an increase in maternal placental and adipose tissue hormones causing decreased phosphorylation of IRS-1 and profound insulin resistance. In most women, the pancreatic insulin secretion increases to meet this demand; for those with underlying β-cell malfunction, the result is hyperglycemia. In women with GDM, the insulin resistance of pregnancy is exaggerated, especially if fasting hyperglycemia is present and is related to additional postreceptor defects. Women who develop significant and predictable metabolic abnormalities may themselves be compromised and threaten their offspring's well-being.

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Fetal Macrosomia

Etiological Factors

7

Oded Langer, MD, PhD

If you always do what you've always done, you'll get what you've always gotten.

—Anthony Robbins

We must become the change we want to see in the world.

—Anonymous, sometimes attributed to Mahatma Gandhi

Key Points

- In diabetic women, fetal growth is the result of interaction between the genetic drive to grow and substrate availability.
- Fetal growth during the first and second trimesters accounts for about 20% of fetal weight at delivery; growth drive is primarily genetic.
- Most fetal growth occurs during the third trimester. The growth drive is influenced mainly by environmental and nutritional factors.
- The majority of large and small infants (70%) are constitutional and influenced by genetic factors.
- Fetal insulin clearance occurs mainly in the liver and not through the kidneys and urine.
- Fetal hyperinsulinemia is considered the marker for diabetic fetopathy. The measurement of fetal insulin in amniotic fluid will result in a high false negative rate.

INTRODUCTION

The famous literary and satirical reports of macrosomia were written by the 16th-century monk and physician Francois Rabelais. He told the story of the birth of the "giant" baby Gargantua; many years later, Gargantua's wife dies giving birth to another "giant," Pantagruel, "…who was so amazingly large and heavy that he could not come into the world without suffocating his mother."[1] Ortega in 1891 reported the birth of a 24-pound, 13-ounce male infant.[2] These examples may be anecdotal, but they are the largest babies reported in the literature. Today, there are numerous institutions worldwide with documented claims for their own "infamous" large babies.

The association between maternal diabetes and the large-for-gestational-age (LGA) infant was first described by Allen.[3] In the same year, Koff and Potter[4] reported the experience of the Chicago Lying-In Hospital where delivery of an infant weighing more than 4500 g was frequently attended with serious difficulties resulting in high fetal and maternal mortality rates. Farquhar[5] in describing the infant of a diabetic mother not only used "gigantism" and "visceromegaly" in his narrative but also used very descriptive nonmedical terms: "…plump, sleek, liberally coated with vernix caseosa, full-faced and plethoric. The umbilical cord and placenta share in the gigantism…"

In the United States, close to 450,000 large infants are born annually. In general, birth weight has shown an incremental rise over time that parallels the progression of obesity and diabetes in the general population. There is ample evidence that fetal macrosomia is associated with increased risk of complications for the mother and the newborn. In current obstetrics, the macrosomic fetus represents a frequent clinical challenge. Evidence is emerging that being born macrosomic is also associated with future health risks. The indication is extensive that maternal overweight and associated metabolic changes, including type 2 and gestational diabetes mellitus (GDM), play a central role. This phenomenon may have a "snowball effect" since the likelihood of obstetric complications (shoulder dystocia, trauma, etc.) increases with enhanced weight. Contemporary researchers have reconfirmed that perinatal morbidity and mortality are higher for the macrosomic neonate (weight ≥ 4000 g) than for neonates who are appropriate-for-gestational age (AGA). Antenatal detection of the excessively large fetus may significantly reduce mortality and morbidity rates.[6]

DEFINITIONS

There are several definitions that characterize the large infant. Many of these definitions, rather than providing a general weight threshold associated with pathophysiology and fetal disease, equate weight thresholds linked to specific complications such as shoulder dystocia and cesarean section.[7,8] This narrow perspective precludes the potential morbidity of the macrosomic condition. Macrosomia has also been defined as a birth weight exceeding an

arbitrary limit, and different studies have set the cutoff at various weight values (4000 g, 4100 g, 4500 g, 4536 g, and 5000 g).[9–14] Using the definition derived mainly from the association between the rate of shoulder dystocia and fetal weight category (4500 g) fails to demonstrate the full magnitude of the diabetic fetopathy. Macrosomia, defined as a weight of 4000 g, is the most common weight category cited in the literature. The use of a higher weight threshold will result in fewer cases of macrosomia but will mask the extent of the complications associated with this condition. These definitions are of historical significance; they bear scant relevance to the understanding and continuing developments in today's research on deviant fetal growth.

A more contemporary approach is to use the term macrosomia as a descriptor of fetal disease (e.g., diabetic fetopathy) rather than as a birth weight cutoff. This definition provides the practitioner with an approach to assessing fetal growth and health for clinical decision making rather than the narrower view of fetal weight in isolation. A more inclusive spectrum of diabetic fetopathy would also include measurement of the fetal heart, body composition, and liver size—all of which assist in differentiating between the constitutionally and abnormally large fetuses. In addition, clinical factors such as glycemic profile and obesity need to be included in the overall assessment to maximize a successful delivery (i.e., the whole is equal to the sum of its parts).

Birth percentile using a threshold of ≥90th percentile for a given gestational age results in the birth of approximately 70% of babies who are healthy but are constitutionally large and 30% who suffer from diabetic fetopathy. Moreover, using weight thresholds limits the identification of fetuses compromised by diabetic fetopathy since only late in gestation do these infants reach weights ≥4000 g even when the mother is diabetic. For example, a fetus weighing 3860 g at 35 weeks would not be classified macrosomic by the former definition even though its weight would be greater than the 97th percentile for gestational age. Several standard weight cutoffs are used by obstetricians.[15,16] A national reference of fetal growth was generated using the 1991 US Live Birth File of the National Center for Health Statistics based on more than 3.8 million births.[17] These and other guidelines identify fetal growth more accurately throughout pregnancy to facilitate timely intervention, but still lack the ability to separate between constitutional and disease-related large infants. Furthermore, growth standards are open to several potential errors. A miscalculation of gestational age, even by a few days, may categorize a diabetic infant as LGA rather than as adequate-for-gestational age. Geographic location[15] as well as ethnicity[16] affects infant size. Table 7-1 demonstrates the differences in weight thresholds by different growth standard tables.

In general, the weight standard used in a study needs to reflect that of the study population. For purposes of portraying an accurate picture, both LGA and macrosomic infants should be reported since using the macrosomic weight definition alone will not provide an accurate description of study results. When delivery occurs at 37–38 weeks, it artificially decreases the number of macrosomic infants and minimizes the magnitude of the problem.

CONTROL OF HUMAN FETAL GROWTH

Embryonic cell proliferation and weight increase rapidly during organ embryogenesis, yet 95% of the ultimate weight of the fetus is gained during the second half of pregnancy.[18] Human placental and fetal weights are comparable until approximately 20 weeks of gestation when the rapid growth phase begins in the fetus. After this, fetal growth continually increases to a maximum rate during the third trimester, while placental weight gain does not parallel this increase, suggesting that factors other than the placental transport functions are involved in controlling fetal growth.

During the early phases of organ embryogenesis, control is exercised primarily by the genome. Beyond this point, however, the ultimate growth of the fetus is controlled by a multitude of factors such as nutrients, environmental considerations, and aberrant metabolic states, that is, diabetes. The growth and development of the fetus are regulated by and dependent on numerous factors. They include the maternal uterine environment, the functioning of the placenta, and the availability of nutrients to mother and fetus. For normal pregnancies, a strong correlation exists between birth weight and gestational age. However, an infant who is small at birth may be chronologically and functionally mature, whereas, in pregnancies complicated by diabetes, a neonate of normal term size may be actually preterm. Fetal growth differs from postnatal growth. Fetal growth appears to be constrained, that is, the fetus does not appear to grow to its maximal potential; the constraining influences are primarily maternal in origin.[19]

TABLE 7-1 Percentiles for Birth Weight for Gestational Age

Gestational Age (yr)	Birth Weight (g)					
	50th Percentile		90th Percentile		95th Percentile	
	Alexander et al.	Langer	Alexander et al.	Langer	Alexander et al.	Langer
37	3117	3033	3755	3657	3956	3875
38	3263	3147	3867	3742	4027	3912
39	3400	3260	3980	3827	4107	3997
40	3495	3317	4060	3920	4185	4111
41	3527	3430	4094	4040	4217	4238
42	3522	3473	4098	4111	4213	4309

FETAL GROWTH: LESSONS FROM THE LABORATORY

Animal models for diabetes and specifically diabetes in pregnancy are continually evolving especially for type 1 diabetes. However, for GDM and type 2 diabetes, designing a model is more difficult because it needs to duplicate insulin resistance and relatively decreased insulin secretion, the hallmarks of GDM and type 2 diabetes. A second limitation in these models is that the human placenta is different than those of sheep, mice, and monkeys and, therefore, the responses are varied and not always comparable.

Maternal diabetes has been produced by streptozotocin injection in the pregnant rhesus (*Macaca mulatto*) monkey.[20] The infants born to these monkeys are macrosomic and exhibit the selective organomegaly characteristics of human infants of diabetic mothers.[21] These monkeys appear to be metabolically similar to human infants of diabetic mothers with demonstrable hyperglycemia and hyperinsulinemia. The rhesus monkey model provides experimental verification of the Pedersen hypothesis yet does not prove a cause-and-effect relationship between fetal hyperinsulinemia and fetal overgrowth. The rhesus monkey fetus is hyperinsulinemic and hyperglycemic, differing from the human fetus who is characteristically hyperinsulinemic and hypoglycemic. Thus, the possibility of hyperglycemia induced by excess substrate on fetal growth cannot be excluded in the monkey. Even with the marked fetal hyperinsulinemia and attendant increase in fetal substrate use, fetal glucose concentrations may be maintained by increased glucose delivery from the mother to the fetus.

Susa et al., in a series of studies, evaluated the effect of hyperinsulinemia on the fetus of primates.[22,23] With the use of different concentration levels and, more specifically, in insulin concentrations comparable to those that may be reached in infants of human mothers with poorly controlled diabetes, the authors produced macrosomia and fetal hyperinsulinemia in primates.[24,25] In the low-dose insulin-treated primate group, the insulin concentration was comparable to levels reported in human fetuses of diabetic mothers.[24–26] In the high-dose insulin-treated primate group, insulin concentrations were higher than those observed in infants of diabetic mothers; the primate fetuses were approximately 100 g heavier than their age-matched controls. The excess weight for these two groups over controls was 23% for the low dose and 27% for the high dose.[26]

The fetal rhesus monkey gains weight at the approximate rate of 5 g/d.[27] In insulin-treated fetuses, there is a doubling of weight gain to 10 g/d. The placental weight also increased with insulin treatment but only in the high-dose treated group.[28] Organomegaly, very similar to the human infant of the diabetic mother, was produced in the fetal primates, with significantly increased body, heart, liver, and spleen weight. The lower-dose insulin treatment produced only significant weight gain and cardiomegaly.

A postmortem study of human infants of diabetic mothers from a Scandinavian population reported total body and heart weight increases.[29] These data are evidence that hyperinsulinemia in the absence of elevated growth substrate concentrations stimulates cellular proliferation; when fetal growth substrates are also elevated, both hyperplasia and hypertrophy have been reported. Naeye studied 21 macrosomic infants and demonstrated that body weight was increased 141% relative to controls. His measurements included length, 112%; heart, 174%; liver, 179%; lung and spleen, 127% each; adrenal, 158%; and pancreas, 110%; and the kidneys and brain remained uninvolved. Thus, both hypertrophy and hyperplasia accounted for the organ enlargement.[28] We studied 84 stillbirths of diabetic mothers.[30] The weight of the principal organs of these fetuses were obtained during autopsy and scored using standard weight autopsy tables. Cases of anomalies, multiple births, and severe macerated fetuses were excluded resulting in 59 diabetic stillbirths compared to 59 nondiabetic stillbirths. Cases were stratified into macrosomic (≥4000 g) and nonmacrosomic (≤4000 g) in both groups (Table 7-2). The study revealed a significantly larger placenta for the diabetic versus the nondiabetic mothers of macrosomic infants (808 ± 134 compared to 645 ± 156, respectively). In contrast, no significant difference in placental size was found in the mothers of the nonmacrosomic infants. Finally, fetal organomegaly was demonstrated in all insulin-sensitive tissues of diabetic stillbirths when the mother was hyperglycemic. On the other hand, the organ size of nondiabetic macrosomic and nonmacrosomic infants was within the normal range suggesting constitutional macrosomia.

TABLE 7-2 Mean Organ Percentiles in Relation to Standard Postmortem Weight Table (=100%)

		Langer and Kagan-Hallet[30]		
	Naeye[28]	Diabetes		Nondiabetes
	<4000	<4000	>4000	>4000
Heart	174%	167%	168%	101%
Lung	127%	147%	152%	116%
Liver	179%	114%	163%	97%
Spleen	127%	95%	129%	105%
Brain	100%	90%	96%	100%
Placenta (g)	—	808 ± 134	645 ± 156	581 ± 143

Hypertrophy and hyperplasia account for organ enlargement.

Furthermore, fetal hyperinsulinemia causes increased cellular glucose utilization, which promotes hepatic glycogen deposition, decreased mobilization of lipids, and increased protein production. Insulin stimulates incorporation of amino acids into proteins, and, in diabetic pregnancies, increased fetal uptake of amino acids and protein synthesis and decreased protein catabolism. During the last 12 weeks of gestation, the fetus of a diabetic mother deposits 50%–60% more fat than the fetus of a nondiabetic woman. The fat consumption pattern of the pregnant diabetic mother is unrelated to the subsequent infant adiposity.[31]

GENETIC FACTORS

The preliminary drive to growth is genetic. By mechanisms that remain poorly defined, there is a genetic control of cell growth and differentiation that is the basic determinant of species size at birth. There are two gene mechanisms associated with cellular, tissue, and organism growth. The first involves cellular division leading to tissue hyperplasia, which peaks in human gestation at the beginning of the third trimester.[32] Hyperplasia is dependent on growth-promoting factors and apoptosis (programmed cell death) controlling systems. The second mechanism is increase in cellular size and mass leading to tissue hypertrophy, the main contributor to fetal weight in the third trimester.[33] The range of birth size determined genetically is large, that is, 2830–3900 g at 40 weeks gestation.[34] Regardless of the number of fetuses, uteroplacental constraints appear to become the major factor for growth at approximately 3000–3200 g in normal pregnancy.[19] The difference in fetal size becomes apparent in the third trimester rather than in early gestation.[35] Early in gestation, genetic factors dominate. Fetal growth in late gestation can be considered the result of the interrelationship between the genetic drive to grow and constraining influences that inhibit growth. Exogenous factors are more important in later gestation when variations in birth size are evident. The balance between genetic and exogenous influences (maternal nutrition, placental factors) is probably controlled by fetal hormones.

Fetal genotype accounts for approximately 15% of variations in birth weight because of certain inherited traits.[36] These traits include fetal gender, racial and ethnic characteristics, and paternal and maternal genetic contributions. About 2% of variations in birth weight are attributable to sex chromosomes.[36] Male genotype is associated with increased birth weight. Male infants average 150–200 g or more than females at term.[37] This increase may be the result of the effect of testicular hormones or because of a more marked antigenic difference between the male fetus and his mother. Placentas from male neonates also weigh more than those of females (2% more at 40 weeks).[38] There is a significant maternal influence on fetal size; this contribution has been estimated to be approximately 20%. Maternal height[39] and weight[40] have been shown to be associated with birth weight, while the father's size does not appear to contribute significantly to neonatal size at birth. In contrast, others reported that maternal height did not contribute to birth weight.[41] Others have shown, too, that race, ethnicity, and body mass index (BMI) contribute to fetal weight.[42–44]

In general, there is a slower rate of growth after 30 weeks gestation in twins and after 36 weeks in singleton births. Women tend to bear infants with comparable birth weights and the same gestational age across successive pregnancies. The fetal size increases with each pregnancy up to about the fifth pregnancy and then stabilizes.[45] Therefore, mothers who deliver constitutionally large or small infants are likely to have similar size infants in subsequent pregnancies. This familial birth weight pattern appears to operate primarily through the mother's linkage. This linkage was also demonstrated in animal studies.[46] In diabetic patients, this maternal linkage to birth weight becomes obscured because of failed glycemic control. Therefore, it is metabolic and environmental factors that influence fetal size in each pregnancy.[45]

INSULIN

Fetal hormones translate genetic information into the actual growth stimuli. Several hormones were proposed to have an effect on fetal growth. However, the permissive and/or regulatory roles of each in normal fetal growth are yet to be established. The Pederson hypothesis suggested that fetal growth is the result of maternal hyperglycemia, which in turn causes fetal hyperinsulinemia and excessive fetal growth.[46] Susa et al. confirmed this hypothesis and demonstrated fetal overgrowth in a primate model creating fetal hyperinsulinemia by implanting an Alzet insulin pump.[47] The Pederson theory was further modified after recognition that other nutrients are present in increased concentrations (e.g., amino acids and lipids) that may contribute to fetal hyperinsulinemia.[48] It has also been suggested that women who are characterized by "relative hypoglycemia" on the glucose tolerance test will also have relative maternal hypoinsulinemia and fetal hypoinsulinemia that result in growth restriction rather than over growth.[49–53]

Insulin plays a significant role in postnatal life as an anabolic hormone, mainly in carbohydrate metabolism. In intrauterine fetal life, insulin is the most recognized growth-promoting hormone. However, growth hormone per se does not influence fetal growth during intrauterine life. The fetal pancreas is the only source of insulin in the fetal circulation since the maternal insulin does not pass the human placenta. Insulin is already present at 8–10 weeks gestation but remains relatively inactive until 20 weeks of gestation when the insulin response to glucose becomes evident.[54] The insulin response to exogenous glucose is related to the endogenous glucose levels in the fetal circulation, which mandate the sensitivity of the fetal β-cells.[55] Thus, chronic fetal hyperglycemia accelerates the development of insulin secretory mechanisms, predisposing infants of diabetic mothers to have a mature insulin response.[56] Insulin receptor levels in the human fetal liver become maximal at 19–25 weeks of gestation. However, there is an increased affinity for insulin in late gestation.[57] Insulin receptors in some fetal tissues are characterized by increasing binding capacity for insulin and failure to down-regulate the receptor number in the presence of hyperinsulinemia.[58] Therefore, an abnormal maternal glycemic level prior to the third trimester will not affect the rate of fetal macrosomia and LGA infants. In contrast, the level of glycemia during the third trimester will directly stimulate fetal hyperinsulinemia and fetal overgrowth. Thus, studies reporting an association between first trimester level of glycemia and fetal macrosomia may be the result of patients in poor control at the onset of pregnancy remaining in poor control throughout.

INSULIN-LIKE GROWTH FACTORS

Insulin-like growth factors (IGFs) are a group of peptides with extensive structural homology to proinsulin. In bioassay systems, they have insulin-like activity as well as growth-promoting effects, mainly by stimulation of cellular proliferation. There are two major forms of IGF in the circulation, which are called IGF I and IGF II. The IGFs are produced by fetal tissues and cannot cross the placenta. They are synthesized at multiple sites and probably act on cells near their site of synthesis.

IGF-I and IGF-II exert their biologic effects via receptor-mediated processes comparable to those of insulin. Low-affinity binding exists between IGFs and insulin receptors.[59] Homology also exists between the type I IGF receptor that has a higher affinity for IGF-I than for IGF-II and the insulin receptor with the consequences that cross binding is possible. A second IGF receptor that is not structurally homologous to the insulin or IGF-I receptor binds IGF-II with affinity much higher than for IGF-I and binds insulin very poorly.[60] The relative ratio of these receptors is tissue specific; therefore, the relative potencies of IGF-I and IGF-II differ from those of insulin.[61]

Given the relative insulin-like potency and the 2000- to 3000-fold higher plasma concentration of IGFs, most of the plasma IGF activity must exist in an inactive form.[59,62–64] Most likely, the growth factors (IGFs) act locally, before they are bound by carrier proteins. Their mechanism of action, therefore, should be autocrine or paracrine processes rather than the classical endocrine mechanism. Thus, the IGF plasma levels do not necessarily reflect their physiologic expression or activity.

Evidence suggests that IGFs influence fetal growth: first, studies demonstrate that IGFs are capable of stimulating the proliferation of fetal cells from various species, including humans. Second, both type I and II IGF receptors have been identified and partially purified from fetal tissues. Third, fetal plasma IGFs are of fetal origin; they are not transported from mother to fetus via the placenta. Studies have demonstrated the direct synthesis of IGFs by fetal fibroblasts in several organs such as intestine, heart, brain, kidney, liver, and lung.[65]

Hill et al.[66] demonstrated that cord blood IGF-I and IGF-binding protein-I (IGFBP-I) are correlated with fetal growth. There were decreased levels of IGF-I and increased IGFBP-I levels in growth-restricted infants in comparison to a control group.[67–69] Roth et al.[70] confirmed this concept and reported increased IGF-I concentrations in macrosomic infants in comparison with a control group of appropriate-for-gestational-age infants. There was a significant correlation between cord IGF-I concentrations and birth weight ($r^2 = 0.61$). Cord IGF-II concentrations are related to fetal pancreatic β-cell function. Decreased IGF-II concentrations are related to β-cell apoptosis, whereas increased IGF-II expression inhibits inducible nitric oxide synthase (iNOS), resulting in decreased β-cell apoptosis.[66]

Several studies demonstrated a positive correlation between fetal birth weight and IGF-I. In addition, an association was found between IGFs and placental size.[34,71] In a study in which IGF-I and IGF-II and their binding proteins were measured in utero by cord puncture between 20 and 37 weeks gestation or taken at delivery between 38 and 42 weeks, IGF-I levels were significantly increased in fetuses whose weights were higher than the mean weight. In contrast, fetuses with growth restriction had significantly reduced IGF-I levels, whereas IGF-II levels did not correlate with weight.[67] Both fetal umbilical IGF-I and insulin concentrations are elevated in infants of diabetic mothers and low in growth-restricted neonates.[68]

Finally, the linear relationship between fetal birth weight and IGFs is probably consistent with the possibility that IGFs influence normal fetal growth. Excess fetal weight in humans and primates is found even when IGF levels are in the normal range but the fetus is hyperinsulinemic. Thus, increased fetal insulin levels are responsible for the fetal macrosomia in diabetes in pregnancy.

PLACENTAL HORMONES AND THE REGULATION OF FETAL GROWTH

Although the molecular mechanism that controls fetal growth remains poorly understood, the placenta, through the delivery of blood, oxygen, and vital nutrients to the fetus and clearance of fetal waste products, remains the controlling agent. During early and mid-gestation, maternal food intake increases 10%–15%, intestinal calcium absorption doubles, and first-phase insulin secretion increases 60%. During the first half of pregnancy, insulin sensitivity is preserved; the increase in insulin secretion promotes lipogenesis and limits fatty acid oxidation and facilitates fat storage.[72] During mid-gestation and late gestation, although maternal food intake and fat mass increase, the maternal metabolism is regulated by insulin resistance, thus expediting maternal utilization of free fatty acids as an energy source. Moreover, this facilitates the transport of glucose, amino acids, essential fatty acids, and ketones for fetal growth.

In recent years, the role of several hormones has become evident. Prolactin (PRL) is produced by the mother's pituitary gland and decidua. It binds with high affinity to human chorionic somatomammotropin (CSH) but with low affinity to human growth hormone (GH) receptors, suggesting that it functions as a lactogen rather than as a somatogen during pregnancy. As a result, the mother in mid-gestation and late gestation is suffused with high levels of lactogenic hormones: PRL, CSH, and virtually pure somatogen, placental growth hormone (PGH). CSH and PRL are also secreted into the fetal circulation; PGH can be detected only in maternal blood.[72]

Maternal weight and fat storage facilitate vital fetal growth. Small-for-gestational-age (SGA) children's mothers had lower prepregnancy BMI and less pregnancy weight gain than mothers of AGA children. The mothers of LGA fetuses contributed the opposite effect to their offspring.[41] However, when good metabolic control is achieved, there is no difference in arachidonic and docosahexaenoic acid in the blood of a mother and umbilical vein in type 1 diabetic women, suggesting that the lipid effect is secondary to the maternal metabolic status.[73]

PGH and CSH expression may also modify release of other critical hormones such as insulin or IGF-I, alter the delivery and accessibility of maternal nutrients, and influence the growth of fetal tissues.[74] An increase in maternal BMI or gestational weight gain enhances maternal fat stores and reduces maternal insulin sensitivity prompting pregnancy glucose intolerance. This hyperglycemic state increases placental weight and fetal weight through induction of fetal hyperinsulinemia.[41] Maternal fat reduces plasma adiponectin. This action may occur because

CSH adiponectin suppresses CSH as well as PGH. An increase in CSH in fetal circulation could induce hyperinsulinemia by induction of β-cell replication, thus increasing fetal weight gain.[75] An increase in maternal CSH and stimulation of maternal β-cell replication and insulin production may provide compensation for maternal insulin resistance and preclude the development of GDM.[72] In addition, adiponectin seems to determine fetal growth and adipose tissue accretion, and low molecular weight is more specifically implicated in males, whereas the higher molecular weight isoform may be more important in females.[76]

OTHER HORMONES

Specific growth-promoting factors that directly influence fetal growth have been difficult to identify. Growth hormone of maternal origin appears to have little influence on fetal growth since normal birth weight is obtained after maternal hypophysectomy in a variety of animals[77] and in humans.[78] A correlation exists between infant birth weight and maternal under nutrition when maternal growth factors are dramatically suppressed; however, newborn birth weight is reduced by up to 20%.[79] The role of thyroid hormone and growth hormone in postnatal growth is well established.[80,81] In contrast, these hormones play a minimal role in prenatal growth. Adrenal corticosteroids fulfill a critical role in the induction of maturational processes in specific organ systems such as lung and intestine.

MATERNAL AND ENVIRONMENTAL RISK FACTORS

Certain factors have been empirically associated with fetal macrosomia such as history of large babies,[82] multiparity, maternal obesity (women who are more than 25% overweight or who have a prepregnant weight/height ratio >2.4), excessive weight gain (more than 35 pounds) during pregnancy, postmature pregnancy (greater than 294 days), and prolonged and/or difficult labor.[83] Chervenak et al.[84] studied 317 consecutive postdate patients with well-dated pregnancies and found a 26% incidence of macrosomia. The incidence of cesarean section for arrest-protraction disorders was 22%. Patients with nonmacrosomic infants had a significantly lower cesarean section rate (10%).[85] Stallone and Ziel[82] found that the maternal factor most commonly associated with macrosomia was a history of large babies. Modanlou et al.[11] demonstrated that 37% of the mothers of macrosomic infants, excluding diabetics, were obese. These studies substantiate the findings of Chervenak et al.[84] that pregravid obesity is a significant etiologic factor in the development of fetal macrosomia. In addition, the rate of oxytocin augmentation of labor has been found to be significantly higher in deliveries of large infants. Prolonged labor, especially in primigravid women, has been reported in mothers of macrosomic babies.

Perinatal and neonatal mortality and morbidity rates are higher in the macrosomic infant. Modanlou et al.[11] reported that of the 66,000 infants weighting 4500 g or more at birth in the United States each year, approximately 10% require admission to an intensive care nursery. The perinatal morbidity rate is at least twice that of normal-sized infants and mortality rates are at least five times higher.[86]

METABOLIC SUBSTRATE FACTORS

Maternal diabetes is characterized by increased plasma concentrations of glucose, free fatty acids, triglycerides, and some amino acids.[48] Maternal plasma concentrations of glucose, triglycerides, and the amino acids alanine, serine, and isoleucine are correlated with the birth weight of the infants of diabetic mothers.[54] Similarly, excess of substrate (glucose) will result in fetal hyperinsulinemia; inadequate substrate delivery to the fetus will be reflected in fetal hypoinsulinemia resulting in growth delay and smaller fetuses. In addition, it has been shown that growth-restricted infants are characterized by hypoinsulinemia, hypoglycemia, and low insulin index.[87] We demonstrated that in the presence of tight glycemic control (≤87 mg/dL), there was more than a 20% incidence of SGA infants.[88] This finding may represent fetal nutrition deprivation resulting in growth delay–related abnormalities. Thus, although tight glycemic control is desirable, the care provider must be alert to preventing overtreatment, which could predispose the fetus to growth restriction.

The growth potential of the developing fetus, under normal conditions, is determined by genetic factors and the adequacy of the maternal uterine environment. This includes the proper functioning of the placental supply line. Any conditions that interfere with this potential impose growth constraints. They may include genetic abnormalities and maternal disease, most significantly diabetes in pregnancy.

Since its recognition 150 years ago, macrosomia has been systematically included as one of the outcome measures in the majority of papers on diabetic fetopathy. Hyperglycemia characteristically exists in the poorly controlled diabetic because of relative hypoinsulinemia. Glucose crosses the placenta by facilitated diffusion, and the fetus maintains a level that represents approximately 75% of the maternal concentration. This imposes a carbohydrate surplus on the fetus, which in response, increases insulin secretion resulting in fetal hyperinsulinemia (Figure 7-1).

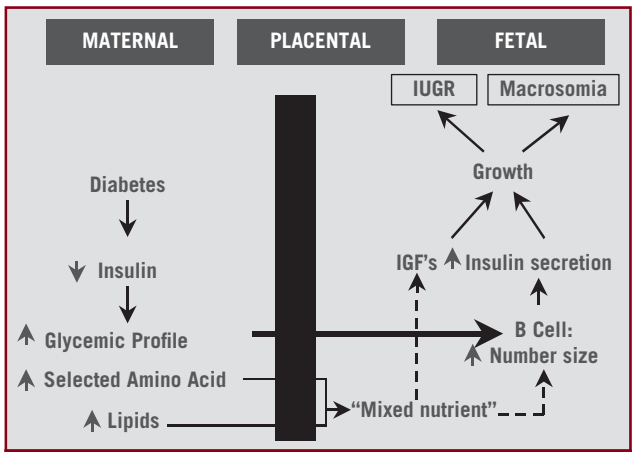

Figure 7-1 The modified Pedersen hypothesis.

FETAL GROWTH PATTERNS IN THE DIABETIC NEONATE

The Gaussian distribution of fetal weight even in the nondiabetic population results in 10% LGA (above the 90th percentile) and 10% SGA (below the 10th percentile). Thus, the majority of LGA and SGA fetuses are either constitutionally large or small but healthy. In pregnant diabetic women, the effect (toxic) of glucose will cause accelerated fetal growth. Therefore, the rate of LGA infants is threefold higher in comparison to the general population.

The growth of the fetal head and femur follows a pattern similar to that of "normal" fetuses. It is after 26–28 weeks of gestation that the abnormal growth patterns become evident and are mostly confined to the abdominal circumference (AC). Ogata et al.[89] studied 23 women with diabetes in pregnancy and showed ultrasonographically that accelerated abdominal growth can be detected at 28–32 weeks gestation and that it diverges from the predicted curve at this stage. Landon et al.[90] studied 31 women with type 1 diabetes mellitus using serial ultrasound examinations in the third trimester and demonstrated a divergent growth pattern (acceleration of AC growth) at week 32 in fetuses destined to be LGA at birth. Langer et al.[91] identified two distinct abnormal fetal growth patterns in the infants of pregnant diabetic women by estimated fetal weight and AC growth velocity throughout the third trimester. The reliability of fetal weight estimation was reflected in the overall error of less than 10%. The results of our study support the existence of both early and late accelerated growth patterns in the fetuses of gestational and pregestational diabetic women. These patterns are inherently different from the growth patterns exhibited by macrosomic fetuses of nondiabetic postdate women. Furthermore, our study described the presence of varied types of delayed growth patterns discernible by sonographic measurements among type 1 diabetes, GDM, and control subjects.

The existence of two distinct excessive growth patterns in the LGA infants was revealed by assessment with serial ultrasonography. At 30 weeks gestation, an early accelerated growth pattern was detected in 23% of the LGA infants; in 77% of these fetuses, the late accelerated growth pattern was observed. Growth escalation began at 33 weeks gestation and reached the 90th percentile at 36 weeks gestation. Head circumference (HC), femur length, and corresponding daily growth rates were comparable for LGA and AGA infants of diabetic mothers. The distinctive factors for identification of the macrosomic infant in utero are an enlarged AC and its corresponding daily growth rate. Other organs affected by the diabetic fetopathy leading to restricted or accelerated growth may be used as potential markers for these deviant growth patterns. These may include subcutaneous fat in the cheek, skin fold thickness, and liver size.[92]

LGA infants of diabetic mothers exhibited a significantly greater daily growth rate in AC than the AGA infants. Within the early accelerated growth pattern, the growth rate for AC remained constant throughout the third trimester. At 30 weeks gestation, the AC was already above the 95th percentile. In infants manifesting the late accelerated growth pattern, acceleration of growth in AC occurred later in the third trimester and reached the 95th percentile at 35 weeks gestation. In this growth pattern, the daily growth rate in AC was significantly greater during the second half of the third trimester (36–40 weeks) than during the first half. Mean blood glucose in the two growth patterns were comparable: 107 ± 16 mg/dL in the early pattern and 116 ± 18 mg/dL in the late pattern. Thus, differences in glycemic profile cannot be attributed to either early or late onset of accelerated growth.[91,92]

As previously discussed, accelerated fetal growth begins in the third trimester. Identification of fetuses in the first and second trimesters at the 90th percentile will suggest genetic influence and constitutional macrosomia rather than diabetic fetopathy. Further confirmation can be made by evaluating insulin levels in the amniotic fluid prior to unnecessary intervention during the 37th to 38th weeks of gestation. The evidence for the presence of fetal hyperinsulinemia will classify the fetus at risk. We demonstrated in over 700 gestational diabetic women with amniocentesis after 37 weeks gestation that the hyperinsulinemic fetuses were several folds at higher risk for neonatal diabetic complications compared to normoinsulinemic fetuses (Table 7-3 and Figure 7-2). However, it is important to note that measurements of amniotic fluid insulin will not identify all hyperinsulinemic fetuses since insulin metabolizes primarily in the liver.

Fat mass accounts for approximately 14% of the birth weight, but explains 46% of the variance in birth weight.[93] In fact infants of mothers with GDM have increased fat mass and percentage body

TABLE 7-3 Comparison between Cord Insulin in Diabetic Patients

	<13 μU	≥13 μU	RR	95% CI
Small for gestational age	3.4%	9.0%	2.1	0.8–5.8
Large for gestational age	9.8%	31.8%	4.3	1.7–10.9
Macrosomia	5.2%	17.9%	2.9	1.2–8.6
Polycythemia	7.1%	14.6%	2.2	1.1–3.5
Hyperbilirubinemia	7.7%	12.5%	1.7	0.9–3.5
Hypocalcemia	5.9%	12.4%	2.2	1.3–4.6
Hypoglycemia	7.2%	22.5%	3.7	2.0–7.0
Intravenous glucose	11.5%	22.6%	5.6	3.7–6.3
NICU	14.2%	23.0%	1.8	1.2–3.1
Number of patients (*n*)	167	262	—	—

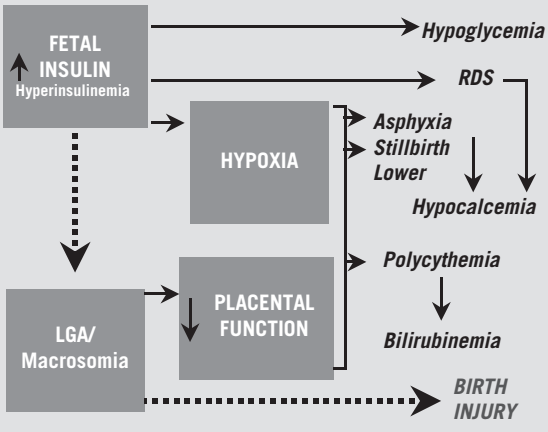

Figure 7-2 Pathogenesis of diabetic fetopathy.

fat (12%–14% compared with 10%–12% in normal infants).[94] The fetal overgrowth, seen in pregnancies complicated by GDM, is the result of many different factors and may lead to overt macrosomia. Several studies have demonstrated that adiposity is higher in infants of diabetic mothers.[95–97] Modanlou et al.[98] described larger shoulder circumference in macrosomic infants of diabetic mothers in comparison to nondiabetic control subjects. Extra fat may be concentrated in the upper body of these infants, and this weight disproportion may increase their risk of shoulder dystocia.

Macrosomic infants of diabetic mothers may have different anthropometric and body composition characteristics than those of nondiabetic patients. Osler[95] described a higher body fat percentile in 12 infants of diabetic mothers but did not indicate whether they were macrosomic. Modanlou et al.[98] showed that the mean weight of macrosomic infants of diabetic mothers was higher than that of control infants and that shoulder circumference was significantly larger. In a study by Ballard et al.[99] infants of diabetic mothers displayed "disproportional macrosomia" defined by increased Ponderal Index more often than infants of nondiabetic mothers.

Brans et al.[97] described thicker skin folds in macrosomic infants of type 1 diabetic mothers in comparison to infants of nondiabetic and type 2 diabetic mothers. Vohr and McGarvey[96] found that LGA infants of diabetic mothers had significantly thicker skin folds than LGA control infants. Although these studies addressed adiposity, they did not describe anthropometric and body composition characteristics in the same macrosomic infants of diabetic mothers. In our study,[100] we described the characteristics that can potentially contribute to shoulder dystocia in macrosomic infants of diabetic mothers: body composition and anthropometric characteristics on the same macrosomic infants.

DETERMINANTS OF NONDIABETIC ABNORMAL FETAL GROWTH

Several conditions associated with fetal macrosomia are found without any relation to diabetes in pregnancy. These conditions are rare and are classified as nondiabetic primary abnormal growth excess of prenatal onset. It is a characteristic of a number of identifiable syndromes, including transposition of the great vessels,[101] Soto's syndrome (cerebral gigantism), Weaver's syndrome, and Beckwith–Wiedemann syndrome (exomphalos-macroglossia-gigantism). The pathogenesis associated with abnormal secondary growth excess of prenatal onset is more widely known than that of primary growth excess. This is mainly due to the presence of diabetes in pregnancy. The most common consequence for infants of diabetic mothers is macrosomia. Early detection of the maternal risk factors associated with fetal macrosomia may alert the physician to the possibility of its occurrence. Beckwith–Wiedemann syndrome is of unknown etiology. Approximately 200 cases have been reported since Beckwith and Wiedemann reported this distinct clinical entity.[102]

Neonates are characterized by macrosomia, macroglossia, linear creases in the external ear lobes and higher than expected incidence of omphalocele. Hydramnios is common and, in spite of a relatively high incidence of prematurity, the birth weight and length average 4 kg and 52.6 cm, respectively. Macrosomia is apparent with large muscle mass and thick subcutaneous tissue. There is accelerated bone maturation and occasional hepatomegaly. Affected fetuses have adrenocortical and pancreatic cell hyperplasia, including an excess of islet cells, primary abnormal growth excess and are born with hyperinsulinemia. Some experience profound neonatal hypoglycemia (about 33%–50% of the neonates) with seizures, apnea, and cyanosis.

Polyerythrocythemia, hyperviscosity, and respiratory difficulty, generally because of macroglossia, are common. There is an unknown incidence of mild to moderate mental deficiency. When the condition is detected and adequately treated in the neonatal period, the mental capacity is apparently normal. Macroglossia becomes less of a problem when growth of the oral cavity enlarges its space relative to the size of the tongue. The excessive rate of growth usually slows after the first few years of life. Beckwith–Wiedemann syndrome should be suspected in any pregnancy in which macrosomia exists without maternal diabetes. Neonatal complications are similar in many respects to those seen in infants of diabetic mothers. Although hyperinsulinemia is not a constant finding in this syndrome, it has been reported that there is an increase in insulin receptor number and affinity in erythrocytes and it has been suggested that the overgrowth may be a consequence of increased tissue responsiveness to normal circulating concentrations of insulin.[103,104] Hypoglycemia in the newborn is usually profound and unrelenting, often resulting in seizures, but is responsive to hydrocortisone analogue therapy. Steroid treatment is usually required for only the first four or five months of life.

An ultrasound examination should be performed to confirm large fetal size and to evaluate for hydramnios in any pregnancy in which macrosomia is suspected. Review of a series of newborns with omphalocele revealed that 11.7% had Beckwith–Wiedemann syndrome.[105] Macroglossia and omphalocele may be detectable by ultrasound, which lends credence to the antenatal diagnosis of Beckwith–Wiedemann syndrome. Although data are not available, it is anticipated that in the fetuses with omphalocele, a hint of the process would be provided early in pregnancy by elevation of the maternal serum α-fetoprotein concentration. Fetal cells in amniotic fluid obtained by amniocentesis should be karyotyped because of the possibility of aneuploidy, and the fluid should also be evaluated for insulin concentration, as outlined earlier, for diagnostic purposes only. There is no evidence that additional insulin provided to the mother would be of any benefit to the fetus.

The growth excess may involve hamartomatous or tumor overgrowth within some of the tissues, such as hemangiomata Wilms'

tumor, adrenocortical tumor, or hepatic tumor. Wilms' tumor occurs in 6.5% of the children with Beckwith–Wiedemann syndrome and may also be responsible for elevated α-fetoprotein concentrations. Serial ultrasound examinations and α-fetoprotein concentration determinations are recommended at 6-month intervals for the first 6 years of life to achieve early detection of tumor development.[106]

Nesidioblastosis refers to a diffuse or disseminated proliferation of pancreatic islet cells. These infants have persistent hyperinsulinemia and hypoglycemia and have disorganized islets with a relative increase in β-cells. It has been postulated that the primary abnormality may be disordered islet organization that prevents the usual paracrine regulation in insulin secretion by other hormones, in particular, by somatostatin, the normal product of the delta cells, present in the islet.[103,107] Without the close relationship of alpha and delta cells, the internal islet control mechanisms are not present and insulin is secreted in unabated fashion. Surgical ablation of up to 95% of the pancreas is the only long-term treatment of nesidioblastosis. The etiology of nesidioblastosis is unclear, but it appears to represent an autosomal recessive disorder of pancreatic development. These infants are phenotypically similar to the infants of the diabetic mother, with macrosomia particularly of adipose and muscle tissue. The condition has been described in five children of both sexes from two families.

Nesidioblastosis should be considered in the differential diagnosis when evaluating a macrosomic fetus. There are no specific ultrasonic criteria for prenatal diagnosis of this entity. One has to proceed in the same way as with the diabetic pregnancy, using ultrasound to confirm macrosomia, amniocentesis for amniotic fluid insulin concentration, and preparation for the delivery of a large fetus. There are no data to indicate a beneficial effect of additional exogenous insulin given to the mother.

Soto's syndrome is sporadic in occurrence, but five families are known in which both parents and offspring are affected. If this means that it is inherited as an autosomal dominant, then the majority of the reported individuals with Soto's syndrome would represent new mutations. The fetus is macrocephalic and dolichocephalic and on close inspection has prognathism with a narrow anterior mandible. Although the fetus is large, the mean term birth weight is only 3.9 kg. Moderate to severe mental retardation is present in 83% of these individuals. There are no reported endocrine abnormalities in Soto's syndrome with the expectation that 14% of neonates have abnormal glucose tolerance tests.[108] Therefore, amniotic fluid insulin concentrations would be expected to be normal or low. Ultrasonic evaluation reveals a large fetus with a greater than normal HC/AC ratio (much like an asymmetrically growth-retarded fetus, but with a higher than expected estimated fetal weight). Prognathism and narrow mandibular development may or may not be detectable by ultrasound.

Weaver's syndrome is a rare syndrome marked by accelerated skeletal growth, camptodactyly, and unusual facies.

SUMMARY

Fetal growth can be considered the outcome of the interaction between the genetic drive to grow and constraints provided by limitations on substrate availability (selected amino acids, free fatty acids, and mainly glucose). Fetal growth restriction may then be viewed as the appropriate adaptation to limited substrate availability to conserve metabolic fuels. In contrast, macrosomia is the result of excess substrate availability, which results in facilitated anabolism leading to increased cell size. The regulation of fetal growth remains poorly understood, and continued research efforts are indicated.

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Fetal Growth Restriction

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8

You should have come to me before.

—Marlon Brando in *The Godfather*

KEY POINTS

- Fetal growth restriction may be the result of various pathologies that need to be considered in the differential diagnosis; of these, placental vascular dysfunction is clinically the most relevant.
- Placental insufficiency is associated with fetal responses in almost every organ system, of which only the cardiovascular and behavioral responses are utilized in clinical management.
- An abdominal circumference (AC) of <10th percentile (reference ranges based on a mixed group of high- and low-risk pregnancies) or <2.5th percentile (reference ranges based on normal pregnancies only) is the most sensitive biometric parameter to detect growth delay.
- Umbilical artery (UA) Doppler is the best method to evaluate the fetal compartment of the placental circulation.
- The combination of a small AC, normal anatomy, low or normal amniotic fluid volume, and abnormal umbilical artery Doppler strongly suggests intrauterine growth restriction (IUGR) due to placental insufficiency. However, the possibility of aneuploidy, syndromes, and viral infection should always be considered and fetal karyotyping should be offered.
- Fetal cardiovascular and behavioral deterioration follows a relatively predictable pattern progressing from early to late changes.
- Direction of surveillance and intervention is inaccurate if based on umbilical artery Doppler alone; examination of the cerebral and venous circulation is mandatory if Doppler surveillance is chosen as the primary management tool.
- For arterial vessels, the pulsatility index offers the narrowest reference limits and measurement error; multiple venous Doppler indices have been described without any clear advantage of individual indices.
- Monitoring intervals should be shortened with progressive cardiovascular compromise.
- Once delivery becomes imminent, antenatal steroids should be administered.
- Delivery should be performed with strong evidence of fetal acidemia and/or impending stillbirth. Ductus venosus (DV) index escalation beyond 3 SDs, or absence or reversal of the DV *a*-wave, are strong evidence of significant fetal compromise. Corroborating evidence from biophysical and computerized heart rate analyses should be sought whenever possible.
- Randomized management studies on venous Doppler for delivery timing of the preterm IUGR fetus are still lacking.
- Diabetes alters several aspects of fetal cardiovascular and behavioral responses, making fetal testing less reliable in diabetic patients.

INTRODUCTION

Disturbance of fetal growth dynamics can result in abnormal weight, body mass, or body proportion at birth. Maternal diabetes is characteristically associated with excessive fetal growth and macrosomia, but diabetic patients may also be at risk for intrauterine growth restriction (IUGR). This risk is related to the degree of maternal vasculopathy and increases with long-standing maternal disease. Although the perinatal management of growth-restricted fetuses with placental insufficiency has evolved markedly over the past five decades, there is scant information on the impact of maternal diabetes on the disease process. The primary focus of this chapter is to review the pathophysiology and perinatal management of growth-restricted fetuses.

Traditionally, abnormal fetal growth was classified by the absolute birth weight as low birth weight (<2500 g), very low birth weight (VLBW, <1500 g), extremely low birth weight (ELBW, <1000 g), or macrosomia (>4000 g). The introduction of population-based birth weight reference ranges was a significant advance, since it allowed the classification of fetal growth patterns by comparing actual birth weight to the expected weight at that gestational age. Lubchenco et al.[1] demonstrated that only the classification of neonates by their birth weight percentile

allows the detection of growth-restricted neonates at increased risk of adverse health events throughout life.[2–4] Accordingly, neonates are now classified as very small for gestational age (VSGA, <3rd percentile), small-for-gestational age (SGA, <10th percentile), appropriate-for-gestational age (AGA, 10–90th percentile), or large-for-gestational age (LGA, >90th percentile).[5] The classification of growth disorders is further enhanced by adjusting birth weight reference limits for pre-pregnancy maternal body mass index, race, birth order, and fetal/neonatal gender (growth potential).[6] Percentiles that are derived in such a way are superior for the prediction of adverse perinatal outcome compared to conventional reference ranges.[7–9] Longitudinal fetal growth patterns, while complicated to study, may help identify more growth abnormalities including the subset of fetuses who remain >10th percentile but have pathologic growth restriction later in pregnancy.[10,11]

The detection of abnormal body mass or proportions is based on anthropometric measurements and ratios that are relatively independent of gender, race, and, to a certain extent, gestational age (and therefore, also birth weight percentiles).[12] The ponderal index [(birthweight (g)/crown-heel length^3) × 100][13] has a high accuracy for the identification of IUGR[14] and macrosomia[15] and correlates more closely with perinatal morbidity and mortality than birth weight percentiles, but may miss the proportionally small and lean growth-restricted neonate.[16,17]

Refining a gold standard that distinguishes between abnormal and physiologic growth patterns at birth is highly desirable for any investigation of the relationship between neonatal size and outcome. From the perspective of the managing perinatologist, only prenatal identification of IUGR is relevant, since it allows appropriate prospective fetal management. Fetal disease, maternal disease, primary placental disease, and extrinsic factors may all interfere with the efficiency of placental nutrient and waste exchange and may therefore result in growth restriction (Figure 8-1). Thus, IUGR is a physical sign rather than a single disease entity, and its impact on outcome is determined by the range of manifestations that are associated with the principal underlying condition. Knowledge of the interactions between etiology, clinical presentation, prognostic factors, and antenatal interventions in pregnancies complicated by growth restriction is required to properly diagnose, assign prognosis, and manage these pregnancies. To formulate a uniform diagnostic and management approach, an understanding of the milestones in normal fetal and placental development and the pathophysiology of disturbed fetal growth is of critical importance.

REGULATION OF FETAL GROWTH

The placenta is the interface between the mother and fetus. Fetal growth is regulated at multiple levels and requires successful placentation for the coordination of key components in the maternal, placental, and fetal compartments.[18] Placental adherence in the first trimester initiates a series of important milestones in the three overlapping gestational epochs. The initiation of placental vascular development permits nutrient and oxygen delivery beyond the capacity of simple diffusion, and therefore, poses few limitations to the growing trophoblast. Maternal adaptations to pregnancy predominate in this epoch. Differentiation of placental transport mechanisms and paracrine and endocrine signaling pathways between the mother, placenta, and fetus continues throughout the second trimester. These steps allow placental growth and establishment of efficient and coordinated nutrient transfer, as well as waste and gas exchange, by completion of the second trimester. This is a prerequisite for third trimester exponential fetal growth and differentiation in preparation for extrauterine life.

Placental adherence is established by the formation of anchoring villi by the cytotrophoblast. These villi eventually connect the decidua and uterus. The maternal circulation gains access to the intervillous space via angiogenesis. Increasing quantities of placental secretory products then appear in the maternal circulation,

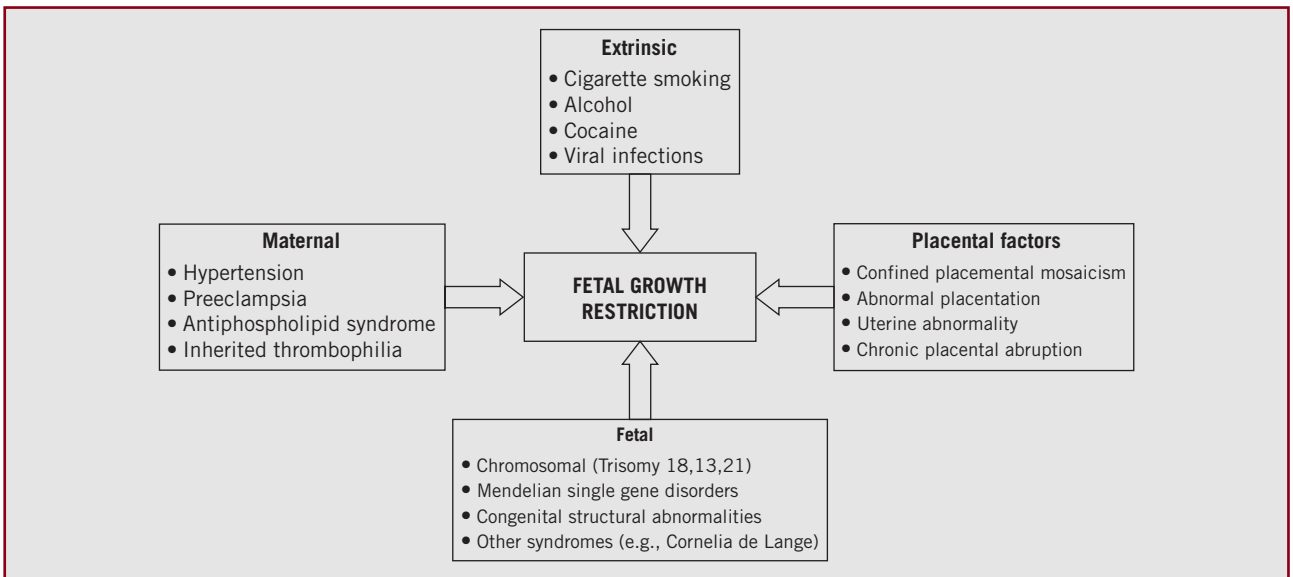

Figure 8.1 This figure shows the principal causes and most common conditions associated with fetal growth restriction (Baschat AA. Pathophysiology of fetal growth restriction-Implications for diagnosis and surveillance. *Obstet Gynecol Survey* 2004; 59:617–27.)

promoting postprandial hyperglycemia, fat deposition, maternal intravascular volume expansion, relative refractoriness of the maternal circulation to vasoactive agents, and increased fasting levels of free fatty acids, triglycerides, and cholesterol. These maternal adaptations increase substrate availability and steadiness of nutrient delivery to the placenta, permitting ongoing placental development. The villous trophoblasts, consisting of maternal microvillous and fetal basal layers, develop as the primary site of nutrient and gas exchange. The efficiency of maternal–fetal exchange depends on four principal factors: (1) the thickness that has to be traversed by diffusible substances, (2) the vascular throughput from the maternal and fetal circulations, (3) the surface area available for exchange, and (4) the elaboration of active transport mechanisms.[18]

By the 16th week of gestation, the villous trophoblast has progressively thinned down to 4 microns, providing little resistance to diffusion. Vascular throughput of the placenta increases in both the maternal and fetal compartments. Extravillous cytotrophoblast infiltration of the maternal spiral arteries results in progressive loss of the musculoelastic media. This process is paralleled in the fetal compartment by continuous villous vascular branching. Significant reduction in vascular resistance and a rapid increase in the exchange area are achieved by 26 weeks gestation and then continue at a slower rate toward term. Under normal circumstances in the term placenta, up to 600 mL/min of maternal cardiac output are delivered to an exchange area of up to 12 m^2. This is matched with a blood flow volume of 200–300 mL/kg/min in the fetal compartment throughout gestation. This magnitude of maternal blood flow is necessary, since maintenance of placental function is energy intensive and consumes as much as 40% of the oxygen and 70% of the glucose supplied to the uterus. Optimal fetal growth and development can only be achieved when the magnitude of maternal nutrient and oxygen delivery to the uterus leaves sufficient surplus for fetal substrate utilization. Perfusion matching between the maternal and fetal compartments is optimized through placental autoregulation. While these developments significantly enhance the efficiency of exchange for diffusible substrate, other substances such as glucose, amino acids, and fatty acids rely on elaboration of active transport mechanisms. Such transport systems develop for each of the nutrient classes and optimize the transfer of glucose, amino acids, and fatty acids across the bilayer.

Each nutrient class has a different role in the fetus. Glucose is the primary oxidative fuel, whereas amino acids are incorporated into proteins. Glucose, and to a lesser extent amino acids, drives the insulin-like growth factor axis and therefore stimulates longitudinal fetal growth. Amino acids are major contributors to protein synthesis and manifest as muscle bulk. Fatty acids are precursors for bioactive compounds including prostaglandins, thromboxanes, and leukotrienes and are also necessary for the maintenance of membrane fluidity and permeability. In addition, long-chain polyunsaturated fatty acids such as arachidonic acid and docosahexanoic acid are essential for normal brain and retinal development. Leptin co-regulates transplacental amino acid and fatty acid transport, and thereby modulates fetal body fat content and proportions. With advancing gestation, the magnitude and efficiency of transfer of these substances increases significantly to provide for placental and fetal growth requirements (Figure 8-2).

Concurrent development of the fetal circulation as a conduit for nutrient and waste delivery is an important cofactor in the fetal growth process. With establishment of a functional circulation, nutrients and oxygen-rich blood from the primitive villous

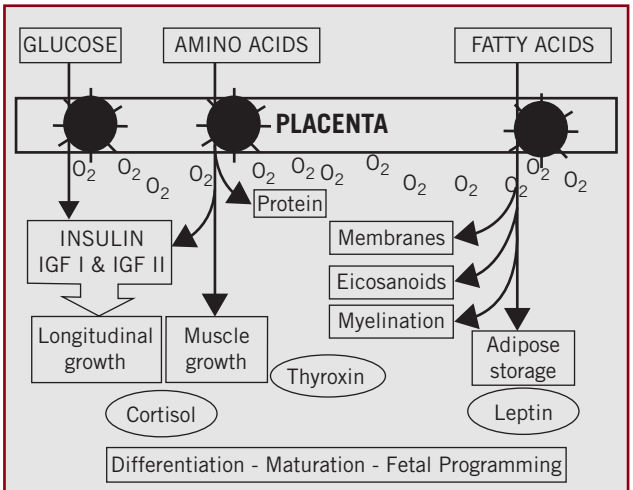

Figure 8.2 In the presence of adequate oxygenation, normal functioning of transplacental transport mechanisms for glucose, amino acids and fatty acids ensure availability of substrate for the fetus. Glucose and amino acids are the main stimulants of the Insulin, IGF growth axis and stimulate longitudinal fetal growth. In addition, amino acids are utilized for protein synthesis and contribute to the muscle bulk. Fatty acids have roles at many levels serving as precursors for eicosanoids and structural components of cell membranes and myelin sheaths. In the third trimester, accumulation of adipose stores provides a reservoir for essential fatty acids. Endocrine axes including hormones such as cortisol, thyroxin, and leptin modulate fetal maturation and differentiation according to substrate availability and may have significant impacts on adult life through fetal programming (Baschat AA. Fetal responses to placental insufficiency: An update. *BJOG* 2004; 111:1031–41.)

circulation enter the fetus via the umbilical vein. The arrangement of the fetal circulation allows further preferential streaming of these nutrients. The ductus venosus (DV) is the first vascular conduit encountered. Through modulation in DV shunting, 68%–82% of umbilical venous blood continues to the liver, while the remainder is distributed to the heart.[19] Differential directionality of blood streams entering the right atrium ensures that nutrient-rich blood is distributed to the left ventricle, myocardium, and brain, while low-nutrient venous return is distributed to the placenta for re-oxygenation and waste exchange. In addition to the overall distribution of left- and right-sided cardiac output, several fetal organs can modify local blood flow to meet oxygen and nutrient demands by autoregulation.

With achievement of these milestones, the prerequisites for normal placental and fetal growth are met. Healthy metabolic and vascular status of the mother promotes steady and enhanced nutrient delivery to the uterus, and placental transport mechanisms allow for efficient bidirectional exchange of nutrients and waste. Under these circumstances, placental and fetal growth across the three trimesters is characterized by sequential cellular hyperplasia, hyperplasia plus hypertrophy, and lastly hypertrophy alone. Placental growth follows a sigmoid curve that plateaus in mid-gestation and precedes exponential third trimester growth of the fetus. During this exponential fetal growth phase of 1.5% per day, initial weight gain is due to longitudinal growth and muscle bulk and therefore

correlates with glucose and amino acid transport, respectively. From 32 weeks onward, fetal fat stores increase from 3.2% to 16% of fetal body weight, accounting for the significant reduction in body water content and preparing the fetus for extrauterine life.[18]

MECHANISMS OF PLACENTAL INSUFFICIENCY

The precise mechanisms underlying how various conditions interfere with normal placentation and culminate in either pregnancy loss or IUGR are still under investigation. Broadly categorized into maternal, uterine, placental, and fetal, the underlying etiologic disorders affect either nutrient and oxygen delivery to the placenta, nutrient and oxygen transfer across the placenta, fetal uptake of nutrients, or regulation of growth processes producing growth restriction that may be characterized by a reduction in fetal size and, when early and severe enough, cell number. Fetal abnormalities (both chromosomal and/or anatomical) and abnormal placental vascular development cause the preponderance of IUGR in singleton pregnancies.[20–24] Generally, the earlier onset of the disease process, the more likely the fetus is to be symmetrically small with a decreased cell number. The etiology of early-onset IUGR is more likely to be a severe maternal vascular disorder, fetal infection, or chromosomal abnormality.[25]

Early interference with placentation affects all levels of placental and fetal development and culminates in the most severe clinical picture. Early first-trimester interference with angiogenesis may prevent successful placental adherence and therefore result in miscarriage. Once placental adherence is achieved, diffusion initially suffices to fulfill embryonic nutrient demands in the first trimester. At this point, interference with vascular maturation and differentiation may compromise placental and fetal nutrition, resulting in miscarriage or stillbirth. If sufficient supply to the placental mass can be established, further differentiation may be possible. Suboptimal maternal adaptation to pregnancy and deficient nutrient delivery pose limitations at all levels of placental function. If too few placental stem villous arteries and terminal villous capillaries develop, IUGR may ensue.[26,27] If trophoblast invasion remains confined to the decidual portion of the myometrium, maternal spiral and radial arteries fail to undergo the physiologic transformation into low-resistance vessels.[28,29] Altered expression of vasoactive substances may increase vascular reactivity, and if hypoxia-stimulated angiogenesis cannot overcome these challenges, placental autoregulation becomes deficient. Maternal placental floor infarcts, fetal villous obliteration, and fibrosis each increase placental blood flow resistance, producing maternal–fetal placental perfusion mismatch that decreases the effective exchange area.[30–33] Feto-placental flow resistance is increased throughout the vascular bed with progressive vascular occlusion, and eventually metabolically active placental mass is reduced.

If adaptive mechanisms permit ongoing fetal survival, early-onset growth restriction with its many fetal manifestations develops. This spectrum of fetal manifestations is determined by the balance of compensatory and decompensatory responses in various organ systems. If compensatory mechanisms are unsuccessful, permanent fetal damage or stillbirth occurs. With successful compensation, the consequences of nutrient shortage may remain largely subclinical, only to be unmasked through its restrictive effect on exponential fetal growth in the second to third trimesters. In these cases, vascular manifestations may be less pronounced and physical characteristics more apparent; a decrease in adipose tissue or abnormal body proportions at birth may be the only evidence.

CONSEQUENCES OF PLACENTAL DYSFUNCTION

When placental dysfunction compromises nutrient delivery sufficiently to trigger fetal mobilization of hepatic glycogen stores, physical manifestations of growth delay become clinically apparent. Liver size is reduced as hepatic glycogen stores are depleted, resulting in a decrease in the abdominal circumference (AC). In addition to this cardinal sign of growth restriction, a range of fetal manifestations of placental insufficiency have been documented in almost every organ system. Of these, metabolic, endocrine, hematologic, cardiovascular, and behavioral responses are best described. Cardiovascular and central nervous system (CNS) responses are best studied in the context of fetal surveillance, because their noninvasive assessment is readily achieved by multivessel Doppler, gray-scale ultrasound, and fetal heart rate analysis. An appreciation of the variety of fetal manifestations is relevant from the perspective of the managing perinatologist and neonatologist. For the perinatologist, this knowledge illustrates the potential limitations of antenatal surveillance. For the neonatologist, it allows anticipation of potential complications that may arise from fetal manifestations persisting beyond the transition to extrauterine life. An appreciation of the range of responses also illustrates how long-term consequences of placental insufficiency may never be completely prevented, even with optimal perinatal management.

METABOLIC RESPONSES

Oxygen and glucose consumption by the placenta is unaltered when uterine nutrient delivery is only mildly restricted and the fetal demands are met by an increased fractional extraction. However, when uterine oxygen delivery falls below a critical value (0.6 mmol/min/kg fetal body weight in sheep), fetal oxygen uptake is reduced and is eventually accompanied by fetal hypoglycemia.[34] The initially mild hypoglycemia results in a blunted fetal pancreatic insulin response, allowing gluconeogenesis from hepatic glycogen stores.[35–38] At this stage, fetal glucose stores and lactate are diverted to the placenta in order to preferentially maintain placental metabolic, endocrine, and nutrient transfer functions. Since hepatic glycogen stores are soon depleted, persistent or declining nutrient deficit results in worsening fetal hypoglycemia and the ability to maintain fetal oxidative metabolism and placental nutrition becomes limited. The use of other fetal energy sources becomes necessary and more widespread metabolic consequences ensue with the significant limitation of oxidative metabolism, downregulation of placental transport mechanisms, and intensifying hypoglycemia. Branched-chain and other essential amino acids are depleted as amino acid transfer becomes limited, and breakdown of endogenous muscle proteins to obtain gluconeogenic amino acids occurs.[39–42] Simultaneously, lactate accumulates due to the limited capacity for oxidative metabolism. Placental transfer of fatty acids is maintained unless there is considerable loss of placental substance. The selectivity of transport mechanisms, particularly for essential fatty acids, may suffer. Fetal free fatty acid and triglyceride levels rise due to reduced utilization, and consequently, there

TABLE 8-1 Summary of Metabolic Responses to Placental Insufficiency

Substrate	Change
Glucose	Decreased proportional to the degree of fetal hypoxemia.
Amino acids	Significant decrease in branched chain amino acids (valine, leucine, isoleucine) as well as lysine and serine. In contrast, hydroxyproline is elevated. The decrease in essential amino acids is proportional to the degree of hypoxemia.
	Elevated amniotic fluid glycine/valine ratio.
	Elevations in amniotic fluid ammonia with a significant positive correlation to the ponderal index.
Fatty acids and triglycerides	Decrease in long-chain polyunsaturated fatty acids (docosahexanoic and arachidonic acid). Decrease in overall fatty acid transfer only with significant loss of placental substance.
	Hypertriglyceridemia due to decreased utilization.
	Lower cholesterol esters.
Oxygen and CO_2	Degree of hypoxemia proportional to villous damage and correlates significantly with hypercapnia, acidemia, hypoglycemia and hyperlacticemia.

is failure to accumulate adipose stores. In this setting of advanced malnutrition, the liver metabolizes the majority of accumulating lactate. However, the fetal brain and heart can also switch their primary nutrient source from glucose to lactate and ketones.[43] Cardiac metabolism has the capacity to remove up to 80% of the circulating lactate.[44,45] Acid–base balance can be maintained as long as acid production is met by sufficient buffering capacity of fetal hemoglobin and a matching removal rate by fetal organs.

Therefore, metabolic compromise progresses through degrees of severity. Hypoglycemia, hypoxemia, and decreased levels of essential amino acids occur first. Increasing hypoxemia, overt hypoaminoacidemia, hypercapnia, hypertriglyceridemia, and hyperlacticemia follow. Lactate production is exponentially correlated to the degree of acidemia that generally results from this metabolic state.[41,46,47] Amniotic fluid evaluation of the glycine/valine ratio and ammonia elevation are additional markers of this state of protein–energy malnutrition.[48,49] Such severe metabolic alterations are more likely with severe, early-onset IUGR, while those fetuses that manifest growth restriction in the third trimester may only have mild acid–base disturbance and subtle changes in lipid metabolism (Table 8-1).[18,50]

ENDOCRINE RESPONSES

The immediate effect of decreased fetal glucose and amino acid levels is the downregulation of the principal endocrine growth axis involving insulin, insulin-like growth factor (IGF) I, IGF II, and leptin-coordinated deposition of fat stores.[51,52] In addition, there is evidence of pancreatic cellular dysfunction through a decreased insulin/glucose ratio and impaired fetal glucose tolerance.[41,53] Elevations in serum glucagon and stimulation of the fetal adrenal axis promote the mobilization of fetal hepatic glycogen stores and peripheral gluconeogenesis in IUGR.[54] Corticotropin-releasing hormone, adrenocorticotropic hormone, and cortisol levels are significantly elevated, relating both to the level of hypoglycemia and to the degree of placental vascular compromise.[41,55,56] However, cortisol elevation downregulates IGF-I activity and may therefore have additional negative impacts on fetal linear growth and potentially on postpartum catch-up growth.[57,58] In addition to the glucocorticoid axis, significant elevations of adrenaline and noradrenaline levels are found in IUGR, while the mineralocorticoid axis appears to remain unaffected.[59–61]

In the IUGR fetus, disturbances at all levels of the endocrine axis can result in hypothyroidism correlating to the degree of hypoxemia.[62,63] Thyroid gland dysfunction may develop as indicated by low levels of thyroxine (T4) and triiodothyronine (T3) despite elevated thyroid-stimulating hormone (TSH) levels. In other instances, central production of TSH may be responsible for fetal hypothyroidism.[64] Finally, downregulation of thyroid hormone receptors may limit the biologic activity of circulating thyroid hormones in specific target tissues such as the developing brain.[65]

There is also evidence of disturbed endocrine regulation of bone formation in IUGR fetuses. Serum levels of active vitamin D and osteocalcin are significantly decreased and may be responsible for the decreased bone mineralization as well as for the decreased bone growth that has been documented in these babies.[66,67]

HEMATOLOGICAL RESPONSES

Fetal hypoxemia is a trigger for erythropoietin release and stimulation of red blood cell production through both medullary and extramedullary sites, resulting in polycythemia.[68–71] The elevation in erythropoietin levels corresponds to the degree of fetal cardiac compromise. Increased extramedullary hematopoiesis may be physiologic until 28 weeks, but can also be induced by prolonged tissue hypoxemia and/or acidosis after this gestational age. Extramedullary sites have larger capillary fenestrations that permit the escape of large nucleated red blood cells (NRBC). Thus, elevated NRBC counts correlate with metabolic and cardiovascular status and are independent markers of poor perinatal outcome.[73–76] While polycythemia and elevations of NRBC counts are typical findings in the majority of IUGR fetuses, more complex hematologic abnormalities suggestive of dysfunctional erythropoiesis are observed with advancing compromise. Fetal anemia despite increased NRBC release and overt decrease in red cell progenitors is observed. These findings could reflect downregulation of pro-erythropoietic cytokines, vitamin B_{12} and ferritin deficiency, or a combination of factors.[77–80]

Coinciding with the abnormalities in red cell indices, platelet counts also decrease. Although platelet-activating factor is inhibited in the placenta,[81] abnormal villous vasculature as indicated by absence or reversal of fetal umbilical artery end-diastolic velocity (see cardiovascular responses below) may pose an overwhelming stimulus for placental platelet activation and aggregation.[82] In the presence of such abnormal umbilical waveform patterns, accelerating cardiac deterioration is associated with lower platelet counts and the incidence of thrombocytopenia at birth increases over tenfold.[83,84] In addition to villous vascular abnormality, the levels of anemia and hypoxemia are independent risk factors for decreasing platelet counts.[85] Increased

whole blood viscosity,[86,87] decreased red blood cell membrane fluidity,[88] and platelet aggregation may be important cofactors for accelerating placental vascular occlusion and dysfunction.

Immune dysfunction in IUGR fetuses may develop at the cellular and humoral levels. Decreases in immunoglobulin and absolute β-cell counts have long been recognized.[89] Reduction in total white blood cell counts and neutrophil, monocyte, and lymphocyte subpopulations occurs.[90] Selective suppression of T-helper and cytotoxic T cells, and smaller ultrasonographic fetal thymus measurements have also been observed.[91,92] These abnormalities are related to the degree of acidemia and help explain the higher susceptibility of IUGR babies to infection after delivery.

CARDIOVASCULAR RESPONSES

Doppler ultrasound is the primary tool used for investigating fetal vascular responses to placental insufficiency. Arterial Doppler waveforms reflect vascular resistance and thus provide information on downstream distribution of cardiac output. Since changes in blood flow resistance relate to vascular structure (e.g., placental histology) as well as to vascular tone (e.g., oxygen-related autoregulation), the information gained depends on the vascular bed examined. The most widely used arterial indices are the systolic/diastolic ratio, the resistance index, and the pulsatility index (PI). The PI has a smaller measurement error, narrower reference limits, and the theoretical advantage of ongoing numerical analysis even when end-diastolic velocity is lost.[93]

The severity of placental vascular dysfunction is reflected in the uterine (maternal compartment) and umbilical (fetal compartment) arteries. The presence of an early diastolic notch in the uterine arteries at 12–14 weeks is the earliest evidence of delayed trophoblast invasion, which is almost certain when "notching" persists beyond 24 weeks.[94,95] Reductions in umbilical venous blood flow volume[96] and increases in multi-gate-measured intraplacental blood flow resistance[97] are the earliest Doppler signs of disturbed fetal villous perfusion. When some 30% of the fetal villous vessels are abnormal, umbilical artery end-diastolic velocity decreases and the Doppler resistance indices become elevated.[98] Absence (AEDV) of umbilical artery end-diastolic velocity or reversal of umbilical artery end-diastolic velocity (RDV) can occur when 60%–70% of the villous vascular tree has been damaged.[99] Increasing Doppler abnormality in the maternal vascular bed identifies patients at risk for preeclampsia, abruption, and IUGR,[100] while abnormal umbilical flows indicate increased risk for fetal hypoxemia and acidemia proportional to the severity of the Doppler abnormality.[101,102]

In the fetal circulation, changes in blood flows are related to placental blood flow resistance, fetal oxygenation, organ autoregulation, and vascular reactivity. The combination of elevated placental blood flow resistance and impaired transplacental gas transfer has several effects. Venous shunting across the DV increases the proportion of umbilical venous blood that bypasses the liver and ultimately reaches the left side of the heart through the foramen ovale. The parallel arrangement of the fetal circulation dictates unique impacts of placental dysfunction on the relative distributions of right and left ventricular output. Elevation of right ventricular afterload (placental resistance) forces redistribution of cardiac output toward the left ventricle and the relative proportion of left ventricular output rises. Through these mechanisms on the venous and arterial sides of the circulation, the supply of nutrient and oxygen-rich blood to the heart and brain can be increased.

In the compensated state, fetal cardiac output is increased and organ autoregulation is maintained.[103,104] Several vascular beds show individual changes in blood flow dynamics. The trunk and cerebral circulations respond differently to hypoxemia. The peripheral arteries constrict in response, and truncal resistance increases as manifested by the elevated umbilical, thoracic, and descending aortic Doppler resistance indices ("hind limb reflex"), which account for most of the increase in right ventricular afterload.[105–108] Conversely, the fetal cerebral circulation dilates in response to hypoxemia. Fetal cerebral vasodilation is reflected in the decline of middle cerebral artery Doppler indices ("brain sparing")[109,110] and acts to decrease the left ventricular afterload. This changing balance between the right and left ventricular afterload results in a decline of the cerebroplacental Doppler index ratio and redistribution of the nutrient-rich left ventricular output to the heart and brain. This is corroborated by direct measurements of cardiac output and progressive decreases in amniotic fluid volume after long-standing redistribution.[105,106,111–113]

Direct evidence of enhanced blood flow to individual organs in response to hypoxemia can be seen in the myocardium,[114] adrenal glands,[115] spleen,[116] and liver,[117] whereas blood flow resistance increases in peripheral pulmonary arteries,[118] the celiac axis,[119] mesenteric vessels,[120,121] kidneys,[122,123] and the femoral and iliac arteries.[124] Overall, these changes complement central blood flow redistribution by enhancing the perfusion of organs vital in fetal life and result in preferential streaming of descending aortic blood flow to the placenta for reoxygenation. In addition, increased levels of endothelin, arginine, vasopressin, norepinephrine, epinephrine, vasoactive intestinal peptide, and atrial natriuretic peptide result in enhanced vascular reactivity that may aggravate the clinical status and increase the complication rate during cordocentesis.[125–127]

Deteriorations of fetal metabolic and cardiovascular status often coincide and are associated with Doppler evidence of declining forward cardiac function and abnormal organ autoregulation.[84,128–130] Examination of fetal cardiovascular status is therefore incomplete without knowledge of cardiac forward function as assessed by venous Doppler. Forward blood flow in the venous system is determined by cardiac compliance, contractility, and afterload, and is characterized by a triphasic flow pattern.[131] The venous flow velocity waveform consists of systolic and diastolic peaks (S- and D-waves) that are generated by the descent of the AV-ring during ventricular systole and passive diastolic ventricular filling, respectively. The sudden increase in right atrial pressure with atrial contraction in late diastole causes a variable amount of reverse flow, producing a second trough after the D wave (*a*-wave). The magnitude of forward flow during atrial systole varies considerably in individual veins. Reversal of flow may be physiologic in the inferior vena cava and hepatic veins, but it is always abnormal in the DV. A decline in forward cardiac function and preload handling marks the onset of cardiovascular decompensation in IUGR fetuses[10–105,132] and is manifested in abnormal venous flow velocity waveforms. Abnormal venous flow is characterized by decreasing forward velocities during the *a*-wave and, to a lesser extent, during the D wave. Multiple venous Doppler indices have been described to characterize this complex waveform without any clear advantage of individual indices.[133,134] Impaired preload handling has been documented in the precordial veins (DV, inferior vena cava,[135] superior vena cava[136]), the hepatic veins (right, middle, and left hepatic[131,137]), and the head and neck veins (jugular veins[138] and

cerebral transverse sinus[139]). If the failure to accommodate preload is progressive, umbilical venous pulsations may be observed and are the ultimate reflection of increased central venous pressure.[140] With advanced circulatory dysfunction, autoregulation may become exaggerated in the coronary circulation[104,114] or nonfunctional in the cerebral and placental circulations.[128,129,141] Ongoing deterioration of cardiac function results in holosystolic tricuspid insufficiency and spontaneous fetal heart rate decelerations, and finally is followed by fetal demise.[142,143] A summary of vascular responses of IUGR fetuses is provided in Table 8-2.

TABLE 8-2 Summary of Vascular Responses in IUGR Fetuses

Doppler Finding	Physiologic Significance
Uterine artery notching	Trophoblast invasion remains limited to the myometrial portion of the spiral arteries. Subsequent failure to fully transform into a low resistance, high capacitance vascular bed increases risk for developing IUGR and/or preeclampsia.
Decreased, absent, or reversed umbilical artery end-diastolic velocity	Abnormal terminal villi and stem arteries result in increased placental vascular resistance and a proportional decrease in the umbilical artery end-diastolic velocity. Associated placental perfusion defects are responsible for impaired feto-maternal gas and nutrient exchange.
Elevation of blood flow resistance in the thoracic aorta and iliac artery	*Hind limb reflex:* Diversion of blood flow away from the carcass at the expense of the lower body. Achieved through increase in right ventricular afterload proximal to the umbilical arteries as well as increased blood flow resistance distally. In addition to centralization (see below), descending aortic blood flow is also preferentially distributed to the placenta.
1. Decrease in the cerebroplacental Doppler ratio. 2. Direct measurement of cardiac output. 3. Reversal of end-diastolic velocity in the aortic isthmus. 4. Absence or reversal of umbilical artery end-diastolic velocity.	*Centralization:* A measurable shift in the relationship between the right and left ventricular afterload, which results in redistribution of cardiac output in favor of the left ventricle (i.e., the heart and the brain). This can be passively mediated purely by an increase in the placental blood flow resistance and therefore right ventricular afterload.
Decrease in the carotid or middle cerebral artery Doppler index.	*Brain sparing:* Cerebral vasodilatation in response to perceived hypoxemia.
Increased superior mesenteric artery Doppler resistance.	During perceived hypoxemia and/or redistribution of cardiac output blood flow to the gut as a nonessential organ in utero is compromised.
Decreased in the splenic artery Doppler index.	Splenic artery vasodilatation enhances perfusion of this important hematopoietic organ possibly facilitating an increase in red cell mass.
Decreased Doppler resistance in the celiac axis.	There may be a reflection of blood flow augmentation in the hepatic and splenic arteries, which are the main branches of this axis.
Increased Doppler resistance in peripheral pulmonary arteries.	As nonessential organs in fetal life, lung perfusion may be further compromised by increased vascular resistance in the pulmonary circulation ensuring that a greater proportion of right ventricular output bypasses the lungs to reach the placenta.
Increased Doppler resistance in the renal arteries.	Redistribution and increased renal vascular tone may be the mediators of oliguria and oligohydramnios observed with chronic and/or progressive hypoxemia.
Measured dilation of the ductus venosus with elevated Doppler index accompanied by decreased hepatic artery Doppler index.	*Liver sparing:* Preferential arterial blood supply to the fetal liver invoked when increased diversion of umbilical venous blood through the ductus venosus jeopardizes hepatic perfusion.
Decreased Doppler index in the adrenal artery flow velocity waveforms.	*Adrenal sparing:* Enhanced adrenal perfusion is triggered as part of the fetal stress response to chronic or acute-on-chronic malnutrition.
Umbilical venous pulsations in association with elevated venous Doppler indices.	Evidence of inefficient forward delivery of cardiac output with subsequent elevation of central venous pressure that is transmitted all the way back into the umbilical vein.
Normalization of cerebral Doppler indices after a period of "brain sparing."	With advanced cardiovascular deterioration, brain autoregulation may become abnormal. Probably in association with a decrease in cardiac function the interval between systolic and diastolic velocities widens resulting in an increase (thus normalization) of the Doppler index.
Sudden ability to visualize and measure coronary blood flow in a setting of deteriorating venous Doppler indices in a premature IUGR fetus.	*Heart sparing:* Marked augmentation of coronary blood flow in situations of acute on chronic hypoxemia that is achieved through upregulation of coronary vascular reserve and vasodilatation.

BEHAVIORAL RESPONSES

Fetal behavioral responses are related to neurodevelopmental status and the impact of ambient oxygen tension on the central regulation of fetal behaviors. Characteristics of the fetal heart rate (FHR) are determined by autonomic control mechanisms superimposed on intrinsic cardiac activity and the effects of oxygen on fetal central regulatory centers. With the maturation of the vasomotor center, reticular activating system, central connections, and increasing processing of peripheral sensory inputs, the characteristics of the fetal heart rate change with advancing gestation. Variations of the heart rate and episodic accelerations coupled to fetal movement each indicate normal functioning of these connections.

Under normal circumstances, successive fulfillment of behavioral milestones progresses from the initiation of gross body movements and fetal breathing to coupling of fetal behavior (e.g., heart rate reactivity) and integration of rest-activity cycles into stable behavioral states (1-4 F). These developments are accompanied by a steadily decreasing FHR baseline (reflecting increasing vagal tone), increasing short- and long-term variability and variation (reflecting increased central processing), and increasing amplitudes of accelerations with advancing gestational age. Once organized behavioral states are established, the diurnal and responsive cyclicity (e.g., to maternal glucose) and their coupling with heart rate reactivity are initiated by 28 weeks of gestation.[144] All milestones are then generally completed by 32 weeks, and heart rate reactivity by traditional criteria is present in 80% of fetuses by this time.

Because variations of fetal behavior may be due to several factors including maturational state, behavioral state, and oxygen tension, observation of several variables over a sufficient time period is necessary to separate physiologic from abnormal variation. The five-component biophysical profile score (BPS) system provides a means to quantify fetal behavior by assessing tone, movement, breathing activity, and fetal heart rate reactivity in an observation period of 30 minutes. Amniotic fluid volume measurement has traditionally been a part of the BPS, providing an indirect assessment of fetal renal/vascular status. In the second trimester, amniotic fluid production is primarily related to fetal urine production and therefore to renal perfusion. Through its relationship with vascular status, amniotic fluid volume assessment provides the main longitudinal monitoring component of the BPS and, accordingly, carries a higher weight in the overall grading of the score. Visual FHR analysis has traditionally been used but poses the problems of inter- and intra-observer variability. These are circumvented by computerized analysis of the fetal heart rate (cCTG). The cCTG assesses short-term, long-term, and mean minute variation in addition to traditional FHR parameters and also allows longitudinal observations.

In IUGR fetuses with chronic hypoxemia and mild placental dysfunction, the primary CNS response is a delay in all aspects of CNS maturation.[145–149] The detection of these early behavioral responses requires sophisticated and/or computerized research tools and therefore cannot be reliably detected by traditional antenatal monitoring. IUGR fetuses typically have delayed acquisition of behavioral milestones. The combination of delayed central integration of fetal heart rate control, decreased fetal activity, and chronic hypoxemia results in a higher baseline heart rate with lower short- and long-term variation (on computerized analysis) and delayed development of heart rate reactivity in IUGR fetuses.[150–153] These maturational differences in fetal heart rate parameters are particularly evident between 28–32 weeks gestation.

Despite the maturational delay of many aspects of CNS function, several centrally regulated responses to acid–base status are preserved. The IUGR fetus maintains behavioral responses to declines in acid–base status. Decreasing global fetal activity initiates the cascade of late behavioral responses to placental insufficiency in the setting of worsening fetal hypoxemia.[154] Fetal breathing movement is typically the first behavioral response to cease with increasing hypoxemia. Gross body movements and tone then decrease until they are no longer observed.[155,156] Traditional fetal heart rate variables are frequently abnormal by this time. Late decelerations of the fetal heart rate may develop due to a relative drop in oxygen tension that exceeds 8 mm Hg (classical late decelerations). Computerized heart rate parameters, especially the short-term variation, may still be maintained in the normal range (above 3.5 milliseconds). Spontaneous decelerations due to depressed cardiac contractility (cardiac late decelerations) typically herald fetal demise.

The sequential loss of these biophysical variables is determined by the central effects of hypoxemia/acidemia independently of the cardiovascular status.[157–161] Reduction of global fetal activity and loss of fetal coupling (loss of heart rate reactivity and fetal breathing movements) are typically observed at a mean pH between 7.10 and 7.20. Abolition of tone and movement is characteristic as pH drops further.[155] In contrast, the declining amniotic fluid volume that commonly accompanies the sequential loss of biophysical variables appears to be related to renal blood flow and the degree of vascular redistribution.[162,163]

MISCELLANEOUS RESPONSES

Several other abnormalities have been described in IUGR fetuses. These include vitamin A, zinc, and copper deficiencies or elevations of the purine nucleotide breakdown product hypoxanthine in correlation with the degree of hypoxemia.[164–168] These alterations further illustrate the diverse fetal impacts of placental insufficiency. It is apparent that IUGR is a complex multisystem disease in which the balance and range of compensatory efforts determines the disease manifestation and progression. Although many fetal responses have been presented in a sequential manner in this chapter, our knowledge on their spectrum and relationships continues to evolve. There appears to be no uniform fetal clinical picture. For example, vascular reactivity, blood viscosity, red cell plasticity, and platelet aggregation determine blood flow dynamics in the placental and fetal circulations. Peripheral blood flow dynamics, metabolic milieu, and filling state of the circulation all influence the efficiency of cardiac forward function and delivery of oxygen, nutrients, and waste to their destined sites. Nutrient deprivation, endocrine imbalance, and hypoxemia potentially alter many aspects of organ function and maturation. Deficient body storage limits available nutrient resources after delivery. It is extremely unlikely that all these factors superimposed on the dynamic process of fetal growth would produce a uniform clinical presentation and progression. The fetal presentation may become even more variable when effects of maternal disease are

superimposed on the fetal condition. Individual fetal assessment tools do not adequately reflect the range of the possible fetal impacts of placental insufficiency. This poses serious limitations to both diagnosis and management of IUGR fetuses and calls for the integration of multiple fetal assessment modalities.

PROGRESSION TO FETAL COMPROMISE

Longitudinal observation of fetal cardiovascular and biophysical parameters offers insight into disease severity and acceleration and, therefore, has implications for planning fetal surveillance. There are cardinal "early" and "late" changes in each monitoring system that progress in a reasonably predictable sequence in 70%–80% of IUGR fetuses presenting before 34 weeks.[163,169,170] Fetal growth restriction that manifests after this gestational age is usually due to milder placental disease producing more subtle cardiovascular abnormalities, while behavioral responses remain related to acid–base status.

When umbilical artery and middle cerebral artery Doppler index deviations are subtle in mild placental insufficiency, a decrease in the cerebroplacental Doppler ratio provides an early and sensitive marker of redistribution of cardiac output and often precedes overt growth delay by up to two weeks.[171] With more marked placental disease, the reduction of fetal growth velocity generally mirrors the elevation in umbilical artery blood flow resistance and is followed by decreasing middle cerebral artery impedance and a decline in amniotic fluid index (AFI). At this time traditional heart rate reactivity may also be lost. The nadir of cerebral blood flow resistance is typically reached after a median of two weeks and is followed by an increase in aortic blood flow impedance.[172,173] Alterations in blood flow patterns across the aortic isthmus, a conduit between the parallel placental and cerebral circulations in the fetus, have been suggested to occur following umbilical and middle cerebral artery Doppler abnormalities and as an intermediate step in the progression from placental insufficiency-induced fetal hypoxemia to fetal cardiovascular decompensation.[174,175] The clinical utility of aortic isthmus flows is currently limited, however. These cardinal "early" cardiovascular responses are considered compensatory since they occur at a time when cardiac function is normal. They are typically accompanied by preferential perfusion of vital organs and the placenta.[169,171,176] At this stage, behavioral and FHR responses primarily reflect delayed maturation of central control mechanisms and are premonitory since they require sophisticated examination techniques for their detection.

Accelerating fetal disease and the onset of decompensation become evident through parallel elevations in placental blood flow resistance and precordial venous Doppler indices (inferior vena cava and DV) that are inversely correlated with fetal heart rate variation and variability.[159,169,170,173] Absence of umbilical artery end-diastolic velocity is characteristic in this setting. With chronic fetal hypoxemia, global fetal activity declines and breathing movements are lost. When fetal compromise accelerates, there is a further steady rise in umbilical blood flow resistance while venous Doppler indices escalate over a wide range.[177] Reversed umbilical artery end-diastolic velocity, overtly abnormal venous Doppler indices, and the development of oligohydramnios are characteristic of this stage of compromise. With ineffective downstream delivery of cardiac output, short-term variation of the FHR becomes abnormal and fetal tone and movements are lost.[170,173] Concurrent evaluation of fetal cardiovascular and biophysical variables indicates that Doppler deterioration precedes an abnormal BPS in the majority of IUGR fetuses.[163] In the final stages of compromise, cardiac dilatation with holosystolic tricuspid insufficiency, complete fetal inactivity, short-term variation below 3.5 milliseconds, and spontaneous "cardiac" late decelerations of the fetal heart rate can be observed as preterminal events.[143,178] This progression may proceed over a median of two weeks but may vary at different gestational ages and with different maternal medical comorbidities.[179–182] These cardinal "late" cardiovascular changes require more advanced Doppler examination techniques, while the biophysical abnormalities become readily recognizable on BPS as metabolic compromise progresses.

RELATIONSHIP BETWEEN FETAL RESPONSES AND OUTCOME

Relationships between fetal testing parameters and subsequent outcome determine the relationships between fetal and neonatal risks and, therefore, are critical for the definition of intervention thresholds. Although prevention of long-term morbidity of IUGR is an attractive goal, there is insufficient information on its relationships with prenatal variables to direct management. Many short-term outcomes have been related to fetal status, but only a few presently appear to be of clinical relevance. Fetal acidemia and major neonatal complications have a significant impact on subsequent neurodevelopment, while the combination of fetal and neonatal deaths determines the overall perinatal mortality.[183] The likelihood for fetal acidemia and stillbirth are, therefore, the strongest fetal criteria for intervention. In contrast, gestational age-specific expectations for neonatal complications and survival often force conservative clinical management. Although multiple fetal and perinatal relationships have been reported, a practical and comprehensive evaluation of the IUGR fetus can be based on the examination of the umbilical and middle cerebral arteries, precordial veins (inferior vena cava, DV), biophysical parameters, and fetal heart rate analysis.

PREDICTION OF ACIDEMIA

Since Doppler parameters are influenced by several variables (i.e., vascular histology, tone, blood pressure), their relationship with acid–base status is not only variable but also dependent on the vascular system examined and the prevalence of Doppler abnormalities and acidemia in the tested population. Brain sparing in the presence of normal venous Doppler parameters is typically associated with hypoxemia but a normal pH. Elevation of venous Doppler indices, either alone or in combination with umbilical venous pulsations, increases the risk for fetal acidemia. This association is strengthened by serial elevations of the DV Doppler index.[177] Depending on the cutoff (2 vs. 3 SD) and the combinations of veins examined, sensitivity for prediction of acidemia ranges from 70% to 90% and specificity from 70% to 80%.[184] Because IUGR fetuses preserve their central responses to acid–base status despite their maturational delay, the BPS and arterial pH remain closely related from 20 weeks onward.[185] An abnormal BPS score of 4 or less is associated with a mean pH < 7.20, and its sensitivity in the prediction of acidemia is 100% for a score of 2 or

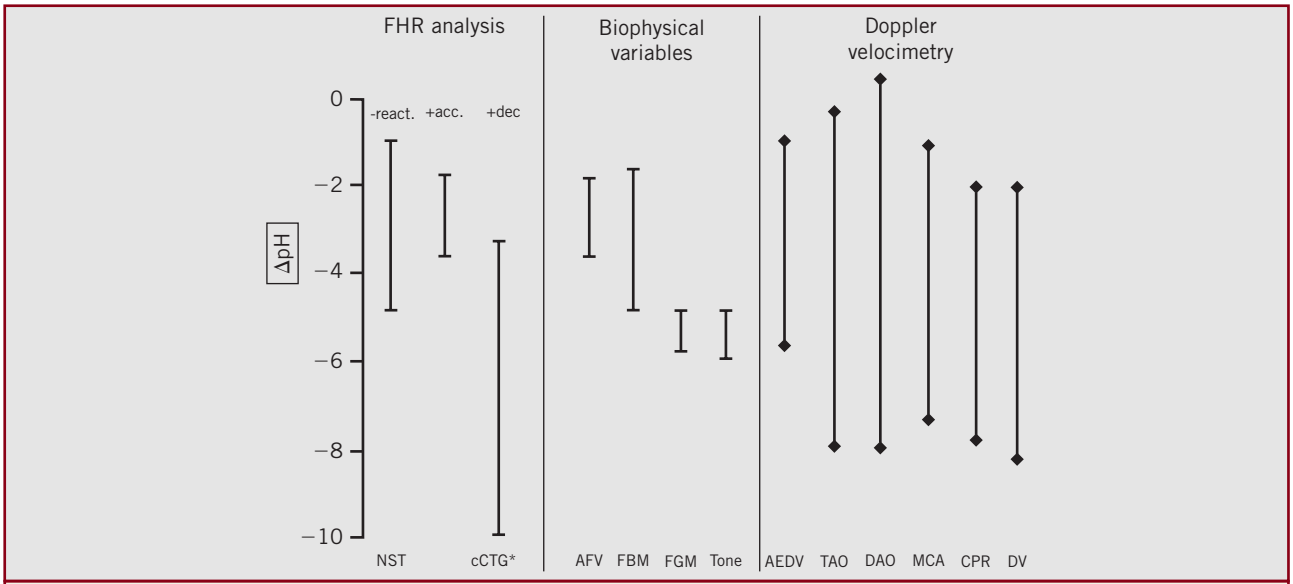

Figure 8.3 This figure displays a diagrammatic representation of pH deviation from the gestational age mean (ΔpH) with abnormal test results in various antenatal tests. These include fetal heart rate (FHR) analysis using traditional non-stress testing (NST, -react= nonreactive) and the computerized cardiotocogram (cCTG, +acc=accelerations present, +dec= obvious decelerations present). Biophysical variables (AFV=amniotic fluid volume, FBM=fetal body movement, FGM= fetal gross movement). The same relationships are expressed for umbilical artery absent end-diastolic velocity (AEDV) and deviation of the arterial or venous Doppler index >2SD from the gestational age mean for the thoracic aorta (TAO), descending aorta (DAO) the middle cerebral artery (MCA), cerebroplacental ratio (CPR) and the ductus venosus (DV) (reproduced with permission from: Baschat A.A. Integrated fetal testing in growth restriction: combining multivessel Doppler and biophysical parameters. *Ultrasound Obstet Gynecol.* 2003; 21: 1–8.).

less. A combination of multivessel Doppler and BPS is, therefore, complementary in the prediction of acid–base status and critical perinatal outcomes.[161] While a nonreactive traditional nonstress test only approaches 50% sensitivity, a computerized documentation of a mean minute variation below 3.5 milliseconds predicts an umbilical artery cord pH < 7.20 with over 90% sensitivity.[186] When the relationship between the various testing modalities and fetal acid–base status is compared, biophysical parameters show a closer relationship with pH and Doppler parameters have a wider variance (Figure 8-3).

PREDICTION OF STILLBIRTH

Abnormal venous flow velocity waveforms are the strongest Doppler predictors of stillbirth. Even among fetuses with severe arterial Doppler abnormalities (e.g., absent/reversed umbilical artery end-diastolic velocity), the risk of stillbirth is largely confined to those fetuses that have abnormal venous Dopplers.[187] The likelihood of stillbirth increases with the degree of venous Doppler abnormality. Venous Doppler findings that are particularly ominous are absence or reversal of the DV *a* wave and biphasic/triphasic umbilical venous pulsations. In the setting of a 25% stillbirth rate in a preterm severe IUGR population, these Doppler findings have a 65% predictive sensitivity and 90% specificity.[188] The duration of the persistent absent or reversed DV *a*-wave, particularly when occurring for over seven days, is a powerful predictor of stillbirth regardless of gestational age.[189] In IUGR fetuses, the BPS deteriorates late and often rapidly, making it unsuitable for the prediction of stillbirth unless daily testing is performed.[190]

PREDICTION OF NEONATAL COMPLICATIONS

Neonatal complications such as respiratory distress syndrome, bronchopulmonary dysplasia, and intraventricular hemorrhage have several determinants. Gestational age is the primary determinant of neonatal complications, followed by birth weight and the degree of growth restriction. Prediction of neonatal variables by fetal status remains imprecise. However, after accounting for gestational age, the impact of fetal Doppler status on neonatal outcomes becomes apparent. Arterial redistribution and brain sparing are not associated with a significant rise in perinatal morbidity. On the other hand, A 2 SD elevation of the DV Doppler index is associated with a threefold increase in major neonatal complications. Further escalation of DV Doppler indices increases this relative risk to 11-fold. The association between the BPS and neonatal morbidity is well documented in a large cohort of patients. The neonatal complication rate of 35% in the presence of an equivocal score rises to as high as 100% when the score deteriorates further.

PREDICITON OF NEONATAL MORTALITY

Neonatal mortality is determined by multiple factors including gestational age at delivery and the occurrence and severity of neonatal complications. The expected neonatal mortality rate in fetuses with umbilical artery (UA) absent or reduced, A/REDV is variable, ranging between 5% and 18% when the venous Doppler indices are normal. An increase in the DV Doppler index doubles this mortality rate, but the predictive sensitivity is only 38% (specificity 98%) in this setting.[20] Although abnormal venous Doppler is associated with a higher rate of neonatal complications, the

ultimate impact on their occurrence and on overall neonatal mortality is a function of gestational age at delivery.

The risk for adverse outcome in IUGR fetuses has traditionally been related to the umbilical artery Doppler waveform. Such an approach no longer stratifies the risk appropriately to direct management. Although the risk for adverse outcome is clearly proportional to the degree of UA Doppler abnormality, meta-analysis indicates that DV Doppler effectively identifies those preterm IUGR fetuses at greatest risk for adverse outcome irrespective of the umbilical artery end-diastolic velocity.

SCREENING AND PREDICTION OF FETAL GROWTH RESTRICTION

The ability to screen for or predict IUGR would be particularly useful in the setting of disease prevention. Over the past decade, substantial research has been dedicated to this topic. Various modalities have been investigated, including the evaluation of first- and second-trimester maternal serum analytes and ultrasound parameters. While lower measurements of first-trimester maternal serum pregnancy-associated plasma protein-A (PAPP-A), ADAM12, and placental growth factor (PlGF) have all been associated with small-for-gestational age fetuses, none has sufficient individual predictive value for IUGR.[191–193] First-trimester ultrasound findings corresponding to SGA fetuses include reduced crown-rump length and slow early fetal growth.[194,195] Certain arterial and venous Dopplers in the first trimester also identify fetuses at risk. Elevations in the uterine artery PI, resistance index, and the presence of diastolic notches have been noted in women whose fetuses ultimately develop IUGR.[196–198] Abnormal fetal DV and umbilical vein Dopplers have also been linked to IUGR.[199,200] In the second trimester, elevations of individual and combined components of the multiple-marker screen are associated with IUGR development. Elevated α-fetoprotein and human chorionic gonadotropin (hCG) are particularly specific in predicting IUGR and may be useful to direct women for ultrasound surveillance for IUGR.[201] Any single biomarker or ultrasound finding is not useful in IUGR prediction models, however, and the ultimate combination of serum and ultrasound markers for adequate prediction remains to be elucidated. More advanced techniques including metabolomics and cell-free fetal DNA quantity in the first trimester are also under preliminary investigation.[202,203]

DIAGNOSTIC APPROACH TO SUSPECTED FETAL GROWTH RESTRICTION

In fetuses with suspected IUGR, a comprehensive diagnostic evaluation is of critical importance, as it is the first step to appropriately direct management. IUGR may be the consequence of various etiologies, and the differential diagnosis always includes maternal disease, placental insufficiency, aneuploidy, nonaneuploid syndromes, and viral infections. Therefore, delayed fetal growth, physical abnormalities, ultrasound markers of aneuploidy, abnormalities of amniotic fluid volume, and disturbed blood flow dynamics may be observed in different combinations based on the underlying disease process. The accurate identification of fetuses that are truly at risk for adverse outcome requires exclusion of small fetuses that are normally grown and those in whom IUGR is due to an underlying condition not amenable to intervention. While maternal disease is readily apparent through a history and physical examination, the accurate evaluation of the possible fetal disorder requires the integration of several diagnostic modalities that evaluate fetal, placental, and amniotic fluid characteristics. Gray-scale ultrasound is the primary diagnostic tool since it allows a detailed fetal anatomic survey, quantification of fetal growth, and assessment of amniotic fluid volume and placental appearance. Although gray-scale ultrasound provides important clues to the presence of IUGR, the liability of preterm delivery and iatrogenic complications is great if the diagnosis is based solely on biometry.[204] It is the combination of fetal biometry with Doppler that is the best available tool for the identification of the small fetus at risk for adverse outcome due to placental insufficiency.[205–208]

An anatomic survey should focus on the exclusion of aneuploidy markers and overt anomalies. Echogenic bowel, nuchal thickening, abnormal hand positioning, gastroschisis, omphalocele, diaphragmatic hernia, and congenital heart defects are examples of ultrasound findings that may be associated with IUGR. Markers of viral infection are nonspecific but include echogenicity and calcification in organs such as the brain and liver.[209] Amniotic fluid volume assessment complements the anatomic survey. Sonographic measurement does not provide an accurate reflection of actual amniotic fluid volume and, by itself, is a poor screening tool for IUGR and fetal acidosis.[210–212] Nevertheless, amniotic fluid volume assessment by either the four-quadrant AFI or the maximum vertical pocket, especially if performed serially, provides an important diagnostic as well as prognostic tool. Faced with small fetal size, abundant amniotic fluid volume is an indication of aneuploidy or fetal infection while normal or decreased amniotic fluid volume is compatible with the diagnosis of placental insufficiency.

Quantification of fetal growth requires accurate knowledge of the gestational age as a reference point to calculate percentile ranks of fetal measurements. An estimated date of confinement (EDC) is based on the last menstrual period when the sonographic estimate of gestational age is within the predictive error (7 days in the first trimester, 14 days in the second trimester, and 21 days in the third trimester). Once the EDC is set by this method or a first-trimester ultrasound, it should not be changed because such a practice interferes with the ability to diagnose IUGR. The fetal AC is related to the hepatic glycogen storage and nutritional state of the fetus, and therefore is the most sensitive and specific measurement for the detection of IUGR.[213–215] Its sensitivity is further enhanced by serial measurements at least 14 days apart.[216] The most accurate AC is the smallest directly measured circumference obtained at the level of the hepatic vein between fetal respirations.[217] If reference ranges for the AC are based on a cross section of small, appropriately grown, preterm and term newborns, the 2.5th percentile is an appropriate cutoff. However, if reference limits are based on healthy women delivering appropriately nourished neonates at term, the <10th percentile cutoff is consistent with IUGR. Concurrent measurement of the head and AC, as well as the femur length, allows calculation of the sonographically estimated fetal weight. An estimated fetal weight below the 10th percentile for gestational age has a lower sensitivity than the AC (85% vs. 98%) but a higher positive predictive value (51% vs. 36%).[215] IUGR fetuses with overall growth ≤10% in combination with measured AC ≤10% have the worst perinatal outcomes.[218]

The next diagnostic step evaluates feto-placental vascular function and is critical for the documentation of placental vascular insufficiency. Randomized trials and meta-analyses confirm that the use of umbilical artery Doppler for this purpose

significantly reduces perinatal mortality and iatrogenic intervention, since the documentation of placental vascular insufficiency effectively separates IUGR fetuses that require surveillance and possible intervention from constitutionally small fetuses.[219–221] An even more comprehensive assessment of feto-placental vascular status can be achieved through the combined examination of the uterine, umbilical, and middle cerebral arteries. Qualitative waveform analysis of the uterine artery (for presence of notching) and the umbilical artery end-diastolic velocity (for positive, absent, or reversed flow) is both simple and effective. For semiquantitative waveform analysis, angle-independent indices are used. Of these, the PI offers the smaller measurement error, narrower reference limits and the possibility for ongoing numerical analysis even when end-diastolic velocity is absent.[222,223] In fetuses presenting with IUGR due to placental insufficiency before 34 weeks gestation, the umbilical artery Doppler waveform is frequently abnormal. Beyond this gestational age, umbilical artery waveforms may be normal while cerebral artery "brain sparing" still occurs with perceived hypoxemia.[224] Therefore, the middle cerebral/umbilical artery Doppler ratio (cerebroplacental ratio) may be abnormal in fetuses with mild placental disease.[225] Beyond 34 weeks gestation, a decrease in the middle cerebral artery Doppler index or the cerebroplacental ratio should therefore heighten suspicion for IUGR even if the umbilical artery blood flow is normal.

Once IUGR is confirmed, fetal karyotyping should be offered and further specialized tests such as maternal serology (TORCH titers), thrombophilia studies, or amniotic fluid viral DNA testing may be indicated. After nontreatable fetal conditions and chromosome abnormalities have been ruled out, further antenatal surveillance should be instituted based on the severity of the maternal and/or fetal condition. A schematic representation of the diagnostic algorithm is presented in Figure 8-4.

CLINICAL MANAGEMENT IN SUSPECTED FETAL GROWTH RESTRICTION

Following the diagnosis of placental-based IUGR, intrauterine therapy would be ideal at gestational ages where pregnancy prolongation is beneficial to the fetus. Clinically available therapeutic options remain limited. Maternal hyperoxygenation,[226,227] intravascular volume expansion,[228] and hyperalimentation[229] have been reported. Many issues such as patient selection, efficacy, the impact of therapy on outcome, and the testing required to monitor the fetus during therapy have not yet been adequately clarified to justify clinical application these modalities outside of a research setting.

Elimination of potential external contributors such as stress and smoking, as well as encouragement of lateral positioning when resting, are advocated. Although not of proven efficacy, these steps should maximize the maternal uterine blood flow. Hospitalized bed rest should be considered, which has the advantages of positive enforcement of rest and facilitation of daily testing. The decision for inpatient versus outpatient management should be based on the severity of the maternal and/or fetal condition and the local standard of care.

Although low-dose aspirin (81 mg/d) has not been shown to help severe early-onset IUGR, it may be of benefit in patients with mild placental dysfunction.[230,231] In view of its documented safety,[232,233] we typically consider low-dose aspirin therapy once the diagnosis of placental-based IUGR is made.

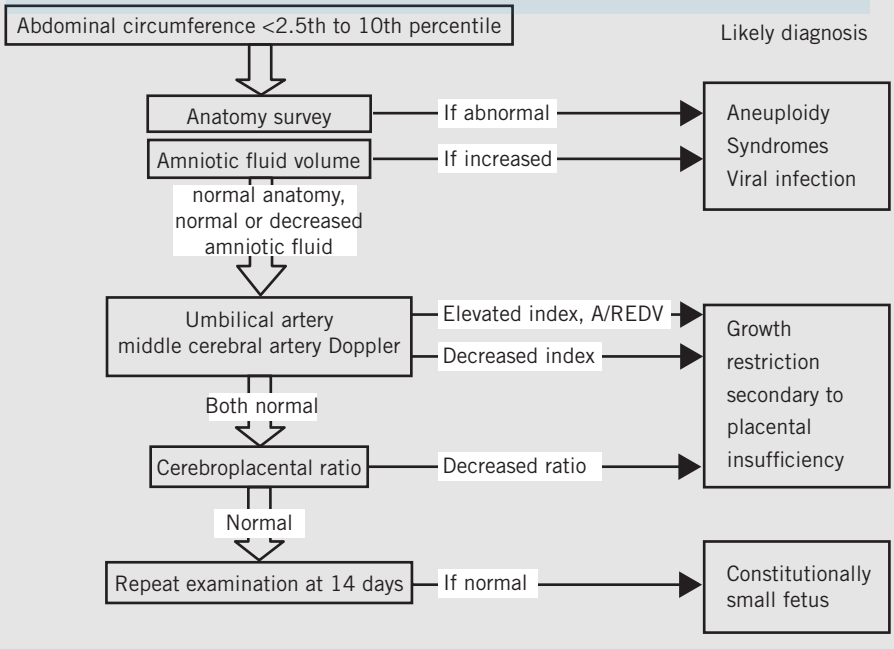

Figure 8.4 This figure displays a decision tree following the evaluation of fetal anatomy, amniotic fluid volume, and umbilical and middle cerebral artery Dopplers. The most likely clinical diagnosis is presented on the right hand side. A high index of suspicion for aneuploidy, viral and non-aneuploid syndrome needs to be maintained. IUGR=intrauterine growth restriction. (Figure 4 in Baschat AA. Pathophysiology of fetal growth restriction-implications for diagnosis and surveillance. *Obstet Gynecol Survey* 2004; 59:617–27.)

Universally available therapeutic options that can positively affect outcome include the antenatal administration of corticosteroids to hasten fetal lung maturity in the preterm fetus and delivery at an institution with a neonatal care unit able to address the management complexities of the IUGR neonate. A complete course of antenatal corticosteroids should be administered to any IUGR fetus in which delivery is anticipated before 34 weeks. A protective effect of intrauterine "stress" against the effects of prematurity is not supported by large population studies of IUGR neonates and therefore does not warrant the omission of steroid therapy.[3,234] In addition, early transfer of a pregnant patient with suspected early-onset IUGR to an experienced perinatal center is strongly suggested in order to assure optimal perinatal therapy. In the absence of any other effective therapies, the main focus in perinatal management is antenatal surveillance in order to minimize fetal risks and to direct the timing of interventions including delivery.

AN INTEGRATED APPROACH TO FETAL SURVEILLANCE IN IUGR

Although IUGR fetuses with placental insufficiency show responses correlating with disease severity in almost every organ system, fetal surveillance is limited to cardiovascular and behavioral evaluation due to its non-invasive nature. The primary assessment tools are Doppler ultrasound, BPS, and fetal heart rate analysis. Since the goal of surveillance is the minimization of perinatal risks to the fetus, it must address two issues: the need for active intervention and the choice of monitoring intervals. The assessment of fetal well-being determines the need for active intervention, while the anticipated rate of progression determines the choice of monitoring intervals. Since the manifestation of fetal disease as well as the rate of progression may be variable, an understanding of the strengths and limitations of individual surveillance tests is important. Arterial Doppler abnormalities typically progress in a characteristic sequence when biophysical and computerized fetal heart rate parameters are still normal. Deteriorating fetal status is reflected in all monitoring systems although the primary manifestation may be variable. The anticipated rate of progression is, therefore, best assessed by Doppler examination of the fetal arterial system. Fetal decompensation can manifest itself in escalation of venous Doppler indices, abnormal BPS, anhydramnios, and an abnormal fetal heart rate.[18,163] While any of the monitoring systems has the potential to detect deterioration, there is increasing evidence that a combination of multiple modalities offers the most comprehensive approach to assessment of fetal well-being.[161]

The need for an accurate assessment of fetal status is of particular importance in circumstances where the thresholds for delivery are high. Although there are surprisingly few randomized management studies that address the issue of delivery timing in IUGR, the growth restriction intervention trial (GRIT) clarifies several important points. In this prospective, randomized, multicenter study of IUGR pregnancies in whom physicians were unsure about delivery timing, more than 500 women were randomized to immediate delivery versus delayed delivery until testing became overtly abnormal. In these pregnancies, timing of delivery had little effect on short-term outcomes although earlier delivery (before 32 weeks) produced a trend toward more disability in early childhood.[235,236] The lack of a relationship between timing of delivery and short-term outcomes suggests that the background morbidity as predetermined by gestational age may not be altered by obstetric management, and/or that physicians already deliver at an optimal time to minimize mortality. At the same time, these data suggest that monitoring and management protocols are insufficient to guide delivery prior to damage of brain development and/or fetal death. This stresses the need for excellent surveillance if conservative management is elected. It was previously shown that clinical management of IUGR fetuses with UA AEDV by daily BPS monitoring with strict delivery indications can prevent stillbirth and acidemia at birth. It is presently unknown if management that is based on multivessel Doppler, BPS, cCTG, or integrated fetal testing will improve short-term outcome in placental-based IUGR across the whole disease spectrum, or if benefits are confined to certain gestational ages.

We utilize a surveillance approach to pregnancies with IUGR due to placental disease that combines Doppler ultrasound and BPS (integrated fetal testing). The testing is always supplemented with maternal assessment of fetal movement ("kick counts"). Doppler examination includes evaluation of the umbilical artery, middle cerebral artery, DV, and free umbilical vein flow velocity waveforms. Monitoring frequencies are adjusted to the fetal condition and depend on the anticipated speed of clinical deterioration and the risk for impending acidemia and/or stillbirth. In fetuses with elevated UA pulsatility, positive end-diastolic flow, and absence of any additional abnormality, weekly BPS and fortnightly multivessel Doppler monitoring is performed. With the onset of brain sparing, Doppler monitoring intervals should be shortened to weekly visits. In fetuses with oligohydramnios or UA AEDV, surveillance every three to four days is suggested. Elevation of the DV Doppler index to >2 SD should prompt surveillance every two to three days. With further increase in the DV Doppler index, daily testing becomes necessary and inpatient admission may be prudent based on local practice. Any change in maternal condition, especially the development of preeclampsia, calls for reassessment of fetal status irrespective of the last examination result (Figure 8-5).

The issue of optimal timing of delivery for IUGR fetuses remains unresolved. By principle, the decision to deliver always weighs fetal versus neonatal risks. Typically, decline in neonatal mortality is greatest between 24 and 28 weeks, while morbidity declines progressively thereafter toward 32 weeks.[237] Perinatal mortality and morbidity is greatest among IUGR fetuses with abnormal venous Doppler indices irrespective of the umbilical artery Doppler waveform. Therefore, basing delivery decision on the umbilical artery waveform alone appears to no longer be appropriate.[238] Delivery is indicated when the risk for fetal acidemia and/or stillbirth is high. This is the case when the DV Doppler index elevation escalates beyond 3 SDs and DV reversed *a*-wave is observed with accompanying umbilical venous pulsations. Other indicators are a BPS less than 6, anhydramnios, fetal heart rate variation below 3.5 milliseconds, or overt fetal distress. The interpretation of test results when the three modalities are in disagreement with each other has not been sufficiently studied. However, a vigorous fetus with normal amniotic fluid volume is unlikely to suffer relevant metabolic compromise even if the venous Doppler index is elevated. Conversely, isolated abnormality of the cCTG is unlikely to be of clinical relevance if all other testing is reassuring. Ultimately, the decision to deliver is critically influenced by gestational age. An ongoing study of prenatally identified IUGR fetuses with elevated placental blood flow resistance suggests that the

IUGR UNLIKELY		
Normal AC, AC growth rate & HC/AC ratio UA, MCA Doppler, BPS & AFV normal	Asphyxia extremely rare low risk for Intrapartum distress	Deliver for obstetric, or maternal factors only, follow growth

IUGR		
AC<5th,low AC growth rate, high HC/AC ratio abnormal UA +/or CPR; normal MCA & venous Doppler BPS ≥ 8/10, AFV normal	Asphyxia extremely rare Increased risk for intrapartum distress	Deliver for obstetric, or maternal factors only. Fortnightly Doppler Weekly BPS
with blood flow redistribution		
IUGR diagnosed based on above criteria low MCA, normal veins BPS≥8/10, AFV normal	Hypoxemia possible, asphyxia rare Increased risk for Intrapartum distress	Deliver for obstetric, or maternal factors only. Weekly Doppler BPS 2 times/week
with significant blood flow redistribution		
UA A/REDV normal veins BPS≥6/10, Oligohydramnios	Hypoxemia common, acidemia or asphyxia possible Onset of fetal compromise	>34 weeks: deliver < 32 weeks: antenatal steroids repeat all testing daily
with proven fetal compromise		
Significant redistribution present Increased DV pulsatillty BPS≥ 6/10, Oligohydramnios	Hypoxemia common, acidemia or asphyxia likely	>32 weeks: deliver <32 weeks: admit, steroids, individualize testing daily vs. TID.
with fetal decompensation		
Compromise by above criteria Absent or reversed DV a-wave, pulsatile UV BPS < 6/10, Oligohydramnios	Cardiovascular instability, metabolic compramise, stillbirth imminent, high perinatal mortality inraspective of intervention	Deliver at tertiary care center with the highest level of NICU care.

Figure 8.5 The management algorithm for pregnancies complicated by fetal growth restriction is based on the ability to perform arterial and venous Doppler as well as a full five component biophysical profile score. AC = abdominal circumference, AFV = amniotic fluid volume, A/REDV= absent/reversed end-diastolic velocity, BPS=biophysical profile score, CPR=cerebroplacental ratio, DV=ductus venosus, HC = head circumference, MCA=middle cerebral artery, NST = nonstress test, NICU =neonatal intensive care unit, TID= three times daily, UA=umbilical artery. (Figure 8 in Baschat A.A., Hecher K. Fetal growth restriction due to placental disease. *Semin Perinatol* 2004; 28:67–80.)

effect of gestational age overshadows all other perinatal variables until approximately 27 weeks, when survival and intact survival first exceed 50%.[237]

The following approach is therefore suggested. Until 27 weeks gestation and/or with an estimated fetal weight below 500 g, delivery thresholds should be high. Indications for delivery should ideally be based on strong corroborating evidence for fetal compromise from several modalities. Venous Doppler abnormalities with an abnormal BPS provide the strongest evidence in this setting. Patients need to be counseled that the chances for survival and intact survival are poor under these circumstances, even with the highest level of neonatal intensive care. Once these gestational and weight thresholds are passed, improved outcomes can be expected for similar delivery indications. It is currently unknown when this approach can be modified to deliver earlier in order to prevent ongoing fetal compromise. In more than 600 IUGR fetuses delivered prior to 32 weeks, we observed survival and intact survival of 80% after 29 weeks gestation suggesting that this may be a time to individualize intervention thresholds.[239] However, in the absence of randomized proof, such practices need to be discussed in a multidisciplinary setting and should be tailored to local practice.

Since the outlined surveillance approach requires multivessel Doppler as well as BPS, it can only be performed at centers that are familiar with both techniques. Modifications of this surveillance protocol need to address the limitations of such an approach. For example, the BPS alone offers little in the prediction of longitudinal progression. Thus, if BPS is the only surveillance tool, daily testing may be required to assure a good outcome. The conclusion of the randomized TRUFFLE study (Trial of Umbilical and Fetal Flow in Europe) will hopefully clarify if delivery triggered by Doppler versus computerized fetal heart rate analysis has a measureable impact on outcome. Ongoing randomized efforts are necessary to refine our understanding of the relationship between fetal testing variables, interventions, and outcomes.

IUGR AND MATERNAL DIABETES—DIAGNOSTIC IMPLICATIONS

There is relatively little information that pertains to patients in whom placental insufficiency and maternal diabetes coexist. From the pathophysiology point of view and the perspective of clinical management, several potential interactions are of importance. In mothers with type 1 DM, those with preconception vascular disease (retinopathy, nephropathy, hypertension) are more likely to develop IUGR.[240] Since glucose plays a central role in the regulation of longitudinal fetal growth, an increased supply of glucose modifies several important fetal manifestations of placental insufficiency. Growth is accelerated through upregulation of the

insulin-IGF axis and fat deposition is increased through increased leptin concentrations.[241] Increased hepatic glycogen storage and liver volume correlate with maternal HbA_{1c} concentrations and result in larger measurements for the AC.[242]

Despite the accelerated fetal growth generally evident in diabetic patients, the relationship between uterine and umbilical artery flow velocity waveforms and pregnancy complications is maintained independently of glycemic control. Elevated blood flow resistance in the uterine artery as early as the first trimester is associated with an increased risk for subsequent hypertensive disorders and fetal growth restriction.[243,244] Fetal weight is inversely correlated with the umbilical artery Doppler resistance.[245] Elevated umbilical artery Doppler indices in diabetic patients identify a subgroup of fetuses at risk for IUGR and/or adverse outcome.[246–248] In fetuses with established IUGR, glycemic control also does not appear to affect aortic and middle cerebral artery flow velocity waveforms.[249–251] These findings suggest that screening for IUGR by combined assessment of the AC and umbilical and middle cerebral artery Doppler is valid in diabetic patients with one important caveat. Because fetuses of diabetic mothers have larger measurements for the AC, higher percentile cutoffs for the AC may have to be selected (10th, or even 25th). More emphasis may have to be placed on serial growth measurements, and a greater than 20% drop in growth velocity may suggest growth delay even if individual measurements are maintained in the normal range.[252]

MATERNAL DIABETES—ALTERATIONS IN FETAL RESPONSES

Infants of diabetic mothers are at risk for polycythemia that is mediated through increased erythropoietin concentrations in correlation with the maternal HbA_{1c} value.[253] Although buffering capacity of fetal blood is increased, the increased red cell mass may have negative impacts on placental blood flow dynamics.

Fetuses of diabetic mothers are also at risk for acidemia and hyperlacticemia that may develop in the presence of normal oxygen tension and independently of placental vascular status.[254,255] In these fetuses, metabolic derangement may therefore be obscured by their apparent normal growth and failure to demonstrate blood flow redistribution.[256]

Maternal diabetes has a significant impact on the development of fetal cardiac function in addition to the known risks of cardiac malformations with elevated HbA_{1c} levels. Fetuses of mothers with diabetes have higher combined ventricular outputs but the physiologic decrease in right-to-left ventricular output ratio does not occur.[257] Accelerated cardiac growth with interventricular septal hypertrophy or global myocardial hypertrophy may be observed.[258–260] In addition to the increased myocardial muscle mass, there is a delayed or absent development of diastolic function.[261–263] This may be reflected in abnormal myocardial wall motion or abnormal trans-atrioventricular valve flows. Interventricular wall thickness and hematocrit values significantly and independently affect the ratios between early and active ventricular filling from the mitral and tricuspid valves.[264,265] Impaired cardiac forward function may also be manifested by an increased percentage of reverse flow in the inferior vena cava.[266] While these abnormalities may be seen with apparently normal glycemic control, they are more pronounced in poorly controlled diabetics. No other differences in venous flow dynamics have yet been reported, although it is of note that there is no increase in umbilical venous volume flow despite the increase in liver volume and body mass.[267]

The sum of these changes has important implications for the fetal cardiovascular system if the challenge of placental insufficiency is superimposed. Since the relationship between right and left ventricular outputs is abnormal, the ability for central redistribution of cardiac output may be limited. Regulation of organ perfusion, therefore, has to rely more on autoregulation. Diastolic function may decompensate earlier, posing limitations to effective downstream delivery of cardiac output. And lastly, increased venous shunting across the DV may leave a larger volume of liver underperfused with subsequent limitations to organ function.

Maternal diabetes also affects behavioral development and biophysical variables. A delay in the development of behavioral milestones is related to the severity of maternal diabetes.[268] Similarly, milestones in fetal heart rate control are delayed. On computerized analysis this is manifested by increased basal heart rates, smaller amplitudes of accelerations with movement, decreased numbers of high variations, and decreased short-term variation.[269,270] Even in the traditional NST, a significant negative correlation between the glycemic control and the heart rate variability has been described.[271]

IUGR AND MATERNAL DIABETES—MANAGEMENT IMPLICATIONS

Although it appears that fetuses with placental insufficiency are most likely to react similarly in the presence of maternal diabetes, it is clear that their compensatory mechanisms are limited. These fetuses are most notable for their risk of having metabolic compromise in the absence of any other signs. There is no information how such fetuses should be managed. Conflicting results from several studies suggest that none of Doppler, BPS, or fetal heart rate analysis appear to be satisfactory if used alone.[272–275] In addition to the management scheme outlined in Figure 8-5, the following modifications are suggested: (1) the diagnosis of IUGR should be based on serial examinations even if the AC is above the 10th percentile (see above), (2) monitoring intervals may need to be shortened, especially if there is a change in the maternal condition, and (3) patients with diabetes have to be aware that sudden fetal death can occur without any premonitory signs.

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SECTION II The Scientific Rationale For the Management of Diabetes in Pregnancy

PART I Outcome Measurements of Diabetes in Pregnancy

The Infant of the Diabetic Mother

Short-Term Implications and Management

9

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One cool judgment is worth a dozen hasty councils. The thing to do is to supply light and not heat.

—Woodrow Wilson

Key Points

- Early growth delay, major congenital malformations, and abortions are related to periconceptional and first trimester poor glycemic control, while minor congenital malformations are related to poor second trimester glycemic control.
- Macrosomia may be associated with significant obstetrical morbidity such as shoulder dystocia, which may result in severe birth trauma.
- Poor glycemic control in late pregnancy is a significant risk factor for fetal distress and neonatal asphyxia; a team of professionals (physicians, neonatal nurse practitioners, midwives, and/or respiratory therapists) trained in the pediatric management of complicated deliveries should be present in the delivery room.
- Glucose monitoring should be initiated as soon as possible after birth, within 2 hours and before feeding, or at any time in which there are abnormal signs. Whenever possible, early enteral feeding should be instituted. Serum calcium and magnesium concentrations should be measured at their physiologic nadir (24 hours of age), while screening for polycythemia should be performed at 2–4 hours of age.
- The differential diagnosis of respiratory symptoms in an infant of diabetic mother should include transient tachypnea of the newborn, respiratory distress syndrome, and asymmetric septal hypertrophy.

INTRODUCTION

In spite of the tremendous improvements in prenatal care and the management of diabetes during pregnancy, the perinatal survival rate of infants of diabetic mothers (IDMs) is still not identical to that of infants of nondiabetic mothers and significant morbidities are still observed.[1] Specifically, the perinatal complications can be traced to inadequate glycemic control during key periods of the pregnancy.[1] For instance, poor glycemic control in the periconceptional period and the early first trimester are predictive of spontaneous abortions, early growth delay, and major congenital malformations.[1] Poor glycemic control during the second trimester of pregnancy is highly predictive of the development of pregnancy-induced hypertension (PIH) and its complications, preterm labor, and all the complications of premature delivery as well as the development of minor congenital anomalies.[1] Poor glycemic control during the third trimester of pregnancy is highly predictive of macrosomia and its associated complications of birth trauma, fetal dystocia, and maternal trauma and high cesarean delivery rate[1] (Figure 9-1). It is also predictive of the complications linked to fetal hyperinsulinism such as neonatal hypoglycemia, respiratory distress, and cardiac septal hypertrophy[1] (see Figure 9-1). Also, poor glycemic control during the third trimester of pregnancy is linked to disturbed fetal oxygenation that may express itself through neonatal depression, fetal distress in labor, and the worst cases of fetal or neonatal death[2] (see Figure 9-1). Finally, hyperglycemia in labor aggravates the risk of neonatal hypoglycemia and is associated with lowered Apgar scores.[2,3] Thus, there is no period during the diabetic pregnancy that allows for inadequate glycemic control, which in all cases bares the risk of being highly consequential. This chapter will review the aforementioned neonatal complications of pregnancy in diabetes and their management.

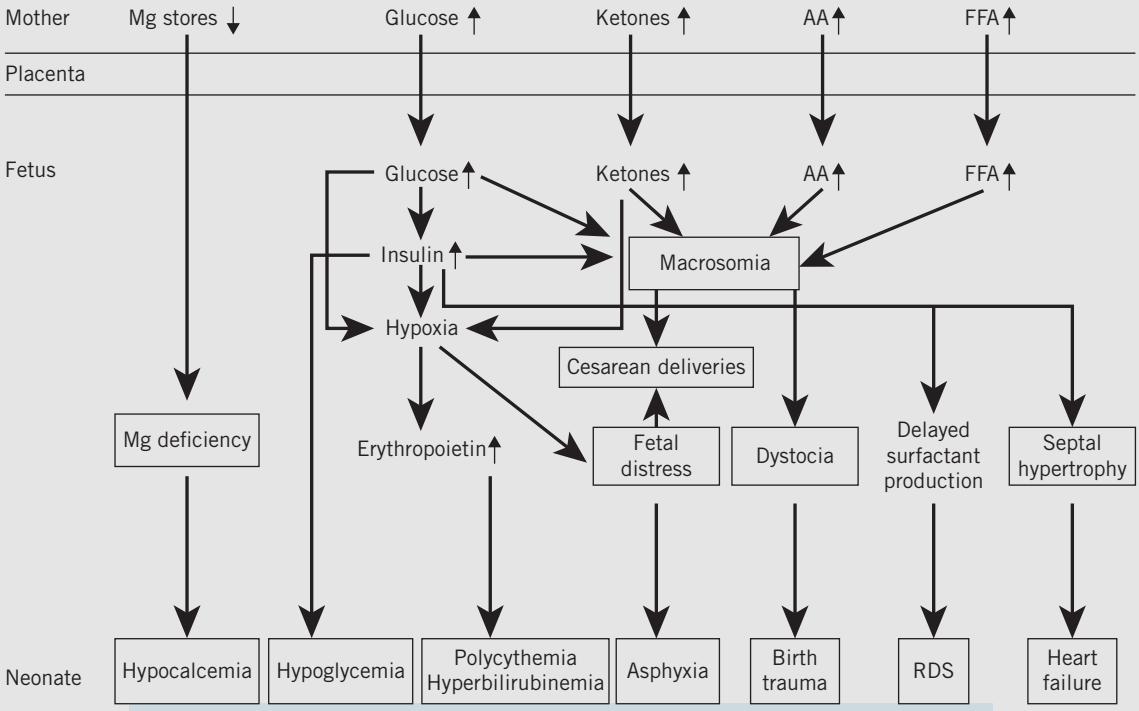

Figure 9-1 Comprehensive scheme of neonatal complications due to poor third-trimester glysemic control (expanded Pedersen hypothesis). Abbreviations: Mg, magnesium; AA, amino acids; FFA, free fatty acids; RDS, respiratory distress syndrome.

THE PATHOPHYSIOLOGY OF NEONATAL COMPLICATIONS IN THE IDM

Early Growth Delay, Major Congenital Malformations, and Abortions

Pedersen was the first to theorize that the fetus of the diabetic mother is hyperglycemic whenever the mother is hyperglycemic.[4] His theory has been verified in both humans and multiple animal models. Interestingly, it appears that the consequences of embryonic or early fetal (<16–20 weeks) hyperglycemia are strikingly different from those of later hyperglycemia (>20 weeks).[5] Indeed, prior to 16–20 weeks, while the fetal pancreas is capable of synthesizing and secreting insulin, it does not do so in response to glucose stimulus.[6] Thus, during early pregnancy, fetal hyperglycemia is not accompanied by fetal hyperinsulinism.[7] As shown by Freinkel et al.,[8] elevated sugar concentration in the culture medium is highly toxic to cell growth, which may be a significant contributing factor for the early growth delay observed when poor glycemic control occurs early in pregnancy.[5] When present, this early growth delay is highly predictive of congenital malformations.[9] In fact HbA1c values at 14 weeks gestation <7% indicate a low risk of congenital anomalies, but when HbA1c rises from 7%–8.5%, the risk increases to 5%, rising to 22% when HbA1c exceeds 10%.[10,11] Malformations and abortions may be significantly linked in that severe major malformations may not be compatible with intrauterine life and may lead to embryonic or early fetal death.[12] In the past few years, there has been a better understanding about the teratogenic effect of hyperglycemia. It appears that in the early stages of embryogenesis, embryonic structures express glucose transporters, but because the placenta is not yet present, they develop under relatively hypoxic conditions (8%–12% oxygen compared to 21% in the maternal circulation).[13] Hyperglycemia combined to environmental hypoxemia lead to increased production of reactive oxygen species (ROS) and subsequent AMP-dependent protein kinase (AMPK) activation.[14] In turn, AMPK and ROS lead to decreased *PAX3* gene expression.[15] Decreased *PAX3* gene expression leads to a loss of control of p53 protein with subsequent increase in apoptosis.[15] Other factors than hyperglycemia that may also contribute to malformations include maternal–fetal hyperketonemia[16] and maternal magnesium (Mg) depletion, also linked to poor glycemic control.[17] The infant of the diabetic mother is at an increased risk for all known kinds of major malformations. However, some of them may be particularly suggestive of maternal diabetes. For instance, the caudal regression syndrome, an extremely rare malformation, is seen almost exclusively in these infants.[18]

It is unclear whether the so-called small left colon syndrome (SLCS) should be classified among the malformations found in IDMs.[19,20] Clearly, in most cases, SLCS is transient and resolves on its own, precluding the true definition of malformation. In this entity, mostly seen in IDMs, the infants present with delayed evacuation of meconium, abdominal distension, and at times with vomiting. Abdominal X-rays are those of low intestinal

obstruction, with nonspecific gaseous distention of the gut. If performed, barium enema reveals a uniformly narrowed colon from the splenic flexure.[20]

Minor congenital malformations are also more frequent in the IDM than in the general population.[21] Interestingly, the presence of minor congenital malformations has been linked to poor glycemic control in the second trimester of pregnancy, that is at a time when major organs have already been formed, precluding the occurrence of a major malformation.[21] Since gestational diabetes is mostly a disease of the second half of pregnancy, one should not expect an increase in the rate of malformations in the products of pregnancies complicated by gestational diabetes. Surprisingly, there is epidemiologic evidence that this may not hold true, and major congenital malformations in pregnancies complicated by gestational diabetes appear to be related to prepregnancy body mass index (BMI).[22]

MACROSOMIA AND ITS CONSEQUENCES

During the second half of pregnancy, maternal fetal hyperglycemia leads to pancreatic β-cell hyperplasia, which responds to hyperglycemia with an increased insulin production.[4] The combination of hyperglycemia and hyperinsulinism has several consequences: the first one is enhanced growth, which may culminate in significant macrosomia.[23] Both fetal weight and placental weight tend to increase.[24] This macrosomia is not only due to increased fat stores but also is linked to significant visceromegaly, in particular that of the liver, the spleen,, and the heart. Visceromegaly is not only due to organ hypertrophy and may also be due to increased fat storage, such as evidenced in the liver of such infants.[25] The head size is typically not increased, thus during vaginal deliveries a typical complication of maternal diabetes is shoulder dystocia, which may lead to significant fetal trauma (clavicular or humeral fracture and Erb's palsy), maternal trauma, and high cesarean delivery rates.[23–26] Consistent with Pedersen's hypothesis, body composition is normal in term infants born to mothers with well-controlled gestational diabetes mellitus.[27] Moreover, the risk for macrosomia is clearly increased with increasing maternal BMI.[28] Importantly, the risk of macrosomia may not only be affected by the metabolic imbalance of diabetes but also appears to be affected by ethnicity[29] (higher risk of macrosomia in African American and Asian neonates at any given level of maternal BMI) and by gender.[30,31] Indeed, gender determines the actions of adiponectin multimers on fetal growth and adiposity,[30] and the magnitude of the reduction of a newborn's birth weight percentile and neonatal fat mass related to the treatment of mild gestational diabetes mellitus appear greater for male neonates.[31] An exception to Pedersen's model is that a small subgroup of IDMs is affected by growth *restriction*. This group of small-for-gestational-age (SGA) infants generally belongs to mothers with advanced diabetic class, with significant vascular disease, often resulting in maternal hypertension, reduced uterine and placental blood flow, and compromised nutrient and oxygen delivery to the fetus.[32] Importantly, in obese women who undergo bariatric surgery, fetal growth is affected in such a manner that the risk of macrosomia is lowered two to three times and the risk of SGA infants is two to three times higher than in a matched group of women without bariatric surgery.[33] The impact on SGA infants is even higher in the subgroup with gastric bypass.[33]

IMPAIRED FETAL OXYGENATION: PATHOPHYSIOLOGY

In pregnancy complicated by poorly controlled diabetes, there is both *decreased oxygen supply* to the fetus and *increased oxygen consumption* by the feto–placental unit, and both may contribute to fetal hypoxemia. Indeed, fetal oxygen supply may be reduced by a decrease in placental blood flow by as much as 35%–50%,[34] which may be aggravated by severe vascular disease.[34] In diabetic ketoacidosis, maternal hypovolemia and acidosis may further reduce placental blood flow.[35] In addition, the increased affinity of glycosylated hemoglobin (HbA1c) to O_2 may be contributory to decreased O_2 maternal–fetal transfer. It has been calculated that an increase in HbA1c of 1% of the total hemoglobin may cause a decrease in the P50 of approximately 0.3 mm Hg.[36–38] Also, in ketoacidosis, the detrimental effect on oxygen release due to a decrease in 2,3-DPG is counteracted by a lower plasma pH (Bohr effect).[38] However, during the recovery period, plasma pH is corrected within hours, while 2,3-DPG values remain low for days. A subsequent left shift of the oxygen dissociation curve occurs, which may have a significant, deleterious impact on oxygen release.[38] Furthermore, in pregnancy complicated by diabetes, placental oxygen transfer may be affected by additional factors such as a reduction of the villous surface area due to an increase in incidence of fetal artery thrombosis[39] and an increase in the diffusion distance, due to thickened basement membrane (as demonstrated by electron microscopy[40] or by the frequent appearance of villous edema[39]).

Enhanced placental–fetal oxygen consumption may also cause fetal hypoxemia. Several animal models have shown that chronic (1 week) fetal hyperglycemia,[41–43] acute (within hours) maternal[44] and fetal hyperketonemia,[45] acute maternal ketoacidemia,[46] and fetal hyperinsulinemia[47–49] or alloxan-induced maternal diabetes[50] lead to fetal hypoxemia and acidosis. The prevalent theory behind these findings is that in the presence of extra fuels or of hyperinsulinemia, the metabolic rate of the placenta increases together with the oxygen consumption rate depriving the fetus of oxygen.[51] Hay et al. demonstrated using the fetal lamb model that insulin promotes the entry of glucose, thereby increasing glucose utilization and oxidation rates.[48,49] Finally, prolonged labor due to fetal dystocia,[22,23] a consequence of fetal macrosomia,[2,22] has the potential to create an additional hypoxic stress to the fetus, as well as the development of PIH.[51]

CLINICAL CONSEQUENCES OF FETAL HYPOXEMIA IN DIABETES

There is a wide range of clinical consequences, from the feared "sudden" intrauterine death, to mild neonatal depression at birth. After the introduction of insulin in 1921, diabetic women became pregnant at increasing rates, but perinatal mortality was very high and remained so until the 1950s, where it still was about 20%. Nearly half of the deaths occurred antenatally.[52] Before 36 weeks gestation, most intrauterine fetal deaths (IUFDs) were associated with diabetic ketoacidosis, while after 36 weeks, IUFDs were often unexplained and somewhat sudden. The series by Kitzmiller et al. and Tyson and Hock, published in the late 1970s, still revealed evidence of intrapartum distress, low Apgar scores, or both in 25% and 28% of infants, respectively.[52,53]

A large study published by our group in the late 1980s concurred with the aforementioned findings (26.7%).[2] However, in our study, intensive fetal monitoring in late pregnancy combined with relatively strict goals of glycemic control enabled us to limit fetal distress in time and/or intensity in most cases and to maintain low Apgar scores into the mild range of neonatal asphyxia.[2] In our series of 162 deliveries, there were only 2 IUFDs, which were attributed to very poor glycemic control, the presence of preeclampsia, and the mother's failure to comply with the prescribed tests of fetal surveillance.[2] In our study, when the infants with low Apgar scores and/or fetal distress were compared to the control ("nonasphyxiated" infants), mothers in the "asphyxiated" group had new-onset nephropathy during pregnancy more often and were regularly affected by preterm labor.[2] There were no significant differences between the two groups in "long-term" glycemic control (as assessed by measurements of hemoglobin A1c); however, mothers in the asphyxiated group had more frequent hyperglycemia (>150 mg/dL) in labor.[2]

POLYCYTHEMIA AND HYPERBILIRUBINEMIA

Chronic fetal hypoxia leads to an increase in the production of fetal erythropoietin[43] and is probably the principal explanation for the increased rates of polycythemia in IDMs.

In the study by Widness et al.,[54] mean maternal HbA1c during the last month of pregnancy correlated significantly with fetal umbilical venous erythropoietin at delivery; amniotic fluid glucose and amniotic fluid insulin also correlated with umbilical venous erythropoietin.[54] We showed that maternal concentrations of HbA1c at the time of delivery correlate with neonatal hematocrit at birth.[55] Moreover, neonatal polycythemia is six times more recurrent in IDMs than in appropriately matched controls[56] with circulating nucleated red blood cells strikingly elevated in IDMs compared to controls.[56,57] The latter finding is also true in infants of gestational diabetic mothers[58] and in large-for-gestational-age infants born to nondiabetic mothers.[59] In our study of perinatal asphyxia in IDMs, "asphyxiated" infants had higher nucleated red blood cell values (an index of chronic hypoxia) than controls.[2] However, even in infants born without perinatal asphyxia, the mean nucleated red blood cell number was still very high, in comparison with a group of normal infants born to mothers without diabetes.[2] There is recent evidence that amniotic fluid oxidative and nitrosative stress biomarkers correlate with fetal chronic hypoxia in diabetic pregnancies.[60]

The fetal erythropoietic response to hypoxia may occur at the expense of other bone marrow line cells, since IDMs have decreased platelet counts that correlate inversely with the circulating nucleated red blood cell counts.[61] Finally, the increased demands for erythropoiesis may deplete iron stores in the fetus of the diabetic mother who at birth has decreased blood iron and ferritin concentrations and elevated transferrin and free erythrocyte protoporphyrin concentrations.[62–64] Moreover, it has been suggested that the increase in red blood cell mass and the increased erythropoietic rate (including ineffective erythropoiesis) may play a role in the neonatal hyperbilirubinemia frequently observed in IDMs.[3,65] Conversely, we showed that IDMs delivered by cesarean section have lower hematocrits and rates of hyperbilirubinemia than those delivered vaginally.[3]

NEONATAL HYPOGLYCEMIA: PATHOPHYSIOLOGY

From clinical experience, neonatal hypoglycemia in IDMs is probably the most frequent complication of diabetes during pregnancy. The exact incidence of neonatal hypoglycemia is, however, extremely difficult to assess, in particular because of the multiple definitions used to describe it[66] and because its occurrence is highly affected by the degree of maternal glycemic control.[1] Nevertheless, IDMs often have a rapid fall in the concentration of blood sugar in the immediate postnatal period.[3] This decline differs in its pattern, both in terms of speed and depth, from the physiologic decrease of blood sugar observed in normal infants.[67–70] The pathophysiology of hypoglycemia in IDMs can be, for the most part, viewed in the general context of Pedersen's hypothesis.[4] Indeed, hyperinsulinemia (presumably caused by maternal hyperglycemia) has been reported in umbilical cord plasma of IDMs[71] as well as in amniotic fluid obtained during diabetic pregnancies.[72] Hyperinsulinism of IDMs is apparently linked to maternal hyperglycemia during the third trimester of pregnancy since the frequency of neonatal hypoglycemia, as well as the cord blood concentrations of C-peptide, correlate with maternal glycohemoglobin concentrations at delivery[71] and is modulated by maternal glycemia in labor.[3] The importance of the availability of alternate fuels in the hypoglycemia of IDMs should not be underestimated, as the gluconeogenetic response to hypoglycemia appears to be blunted. Their blood concentrations of fatty acids are reduced,[73,74] plasma concentrations of ketones are no different than those of nonhypoglycemic controls,[74] and blood concentrations of plasma amino acids are little, if any, affected by hypoglycemia.[75,76] A reduced postnatal glucagon surge appears to accompany the hyperinsulinism.[77] Thus, it appears that IDMs are, in terms of energy metabolism, in double jeopardy because of frequent decreases in plasma glucose and a relative lack of adequate gluconeogenetic response. Moreover, other risk factors for hypoglycemia exist in the IDM. First, neonatal asphyxia may aggravate hypoglycemia, due to increased glucose demands during anaerobic metabolism.[77] Hypoglycemic IDMs have lower umbilical cord pH than their nonhypoglycemic counterpart.[78] Also, neonatal polycythemia is a known cause of refractory hypoglycemia, presumably because of increased glucose utilization by the red blood cell mass.[79] We showed that polycythemic IDMs have rates of hypoglycemia three times higher than nonpolycythemic IDMs.[56]

DEFINITION AND CLINICAL SIGNIFICANCE

The definition of neonatal hypoglycemia is a matter of great controversy. Many reports have arbitrarily defined it as being a serum, plasma, or whole blood sugar value below 30–50 mg/dL, while it is a known fact that blood sugar determined from the same blood sample will differ whether serum, plasma, or whole blood glucose are measured and will vary with the method of measurement. Furthermore, as pointed out by Cornblath and Scwartz, "normal values" may be defined using many different approaches.[80] One definition describes hypoglycemia statistically as blood glucose concentration more than 2 standard deviations below the mean for a population of full-term well infants. This method is arbitrary and only defines a population at higher risk. Another method is to define hypoglycemia from a metabolic standpoint, that is, the blood glucose concentration at which the counter-regulatory

response becomes activated. Other authors have proposed a neurophysiological definition to neonatal hypoglycemia, based on a threshold blood glucose concentration associated with disturbed neurophysiological function, such as auditory evoked response waveform. Finally, a neurodevelopmental definition has been proposed by Lucas et al.[81] who found a threshold value of 2.5 mmol (47 mg/dL) to be more predictive of lower Bayley scores. Cornblath et al. have recently and extensively reviewed the controversies regarding the definition of neonatal hypoglycemia and have suggested operational thresholds[66] for the purpose of defining and managing neonatal hypoglycemia in IDMs.

DISORDERS OF MINERAL METABOLISM IN IDMS

Similar to the results of animal studies, IDMs have decreased bone density at birth.[82] Decreased bone density in IDMs correlates with decreased bone density in their mothers, but does not appear to be predictive of their serum Ca.[82] Decreased bone density in IDMs appears to be due to increased bone resorption, rather than decreased bone formation.[83] Indeed, indices of osteoclastic activity (such as cord blood telopeptide of type I collagen) are higher at birth in IDMs than in controls, while indices of bone formation (such as cord blood propeptide type I collagen) are similar.[83] The clinical consequences of decreased bone density in IDMs have not been systematically studied, and it is not known whether these infants are at an increased risk for fractures, in particular, obstetrical ones.

Up to 50% of IDMs may develop neonatal hypocalcemia (NHC).[82] Both rates and severity of NHC have been significantly lowered by modern management of glycemic control during pregnancy. Many studies of NHC in IDMs originated from the Program Project Grant of Diabetes in Pregnancy conducted by the authors and other investigators at the University of Cincinnati. Well-established risk factors of NHC are birth asphyxia and prematurity. These two factors play a dominant role in the NHC of IDMs.[84–86]

As previously mentioned, earlier IDMs are at a higher risk of developing birth asphyxia.[2] The mechanisms of asphyxia-induced NHC are multiple and include increased intracellular phosphorus release, usage of sodium bicarbonate to buffer acidosis,[86] and stress-induced calcitonin release.[87] Furthermore, IDMs are at a higher risk of being born early, either because of iatrogenic prematurity (due to maternal or fetal reasons)[2,3] or because of spontaneously occurring preterm labor.[88] Preterm infants have high rates of NHC, due to a combination of factors: increased rate of birth asphyxia,[89] decreased ability to secrete parathyroid hormone (PTH) in response to induced hypocalcemia,[90,91] sustained calcitonin production in the presence of hypocalcemia,[87] and possibly end-organ resistance to 1,25 (OH)2 cholecalciferol (the most active form of vitamin D).[92]

Independent of the asphyxia and the prematurity factor, it appears that Mg deficiency plays an important role in the pathogenesis of NHC in IDMs.[93–104] In poorly controlled insulin-dependent diabetes mellitus (IDDM), glycosuria is accompanied by urinary Mg losses, in both nonpregnant and pregnant patients.[93–95] Maternal Mg deficiency leads to fetal Mg deficiency, as evidenced by decreased amniotic fluid Mg concentrations[95] and in lower cord blood or neonatal serum Mg concentrations in IDMs.[94,95] It is known that Mg is necessary for the appropriate function of the Mg-dependent adenylate cyclase involved in the secretion of PTH, as well as in the Mg-dependent adenylate cyclase involved in the action of PTH on its target cells.[98] Thus, in Mg deficiency, there is a state of functional hypoparathyroidism, combined to end-organ resistance to PTH. In infants, the PTH response to Mg administration correlates inversely with Mg status; in Mg-replete infants, Mg administration leads to an appropriate negative feedback, and a decrease in PTH production and in serum calcium concentrations. Paradoxically, in Mg-depleted infants, Mg administration leads to an increase in PTH production and in serum calcium concentrations.[98] In IDMs, serum Ca concentrations correlate directly with serum Mg concentrations and inversely with maternal HbA1c.[85] Also, IDMs have inadequate PTH elevation in response to hypocalcemia.[84] Their calcitonin concentrations remain elevated at birth, as in every other normal newborn, but this does not appear to play a significant role in the pathogenesis of NHC.[85]

We demonstrated that a protocol of strict management of diabetes in pregnancy is associated with a reduction in the rate of hypocalcemia.[103] Moreover, in a randomized, blinded, controlled clinical trial, we showed that prophylactic administration of intramuscular Mg at birth decreased the intensity of the physiologic drop in serum Ca that occurs after birth.[104] However, in this group of very well-controlled diabetic mothers, as stated earlier, NHC is rare, and prophylactic Mg therapy did not prevent NHC.[104]

PREMATURITY AND RESPIRATORY DISTRESS SYNDROME

Several epidemiologic studies, including the one we performed in the framework of the Program Project Grant at the University of Cincinnati, have revealed that the incidence of spontaneously occurring preterm labor is nearly twice greater in a population of insulin-dependent diabetic pregnant women than in a control population.[88] Moreover, preterm labor in insulin-dependent pregnant women is highly predicted by both poor glycemic control in the second trimester of pregnancy (as evidenced by high glycohemoglobin A1 concentrations) and by the presence of urogenital infections.[88] These two risk factors act in combination and independently. Whether poor glycemic control favors the development of urogenital infection or urogenital infection precipitates the loss of glycemic control is unknown.[88] Nevertheless, the IDM is at risk for prematurity, either due to spontaneously occurring preterm labor or due to iatrogenic prematurity. Indeed, because of intense fetal surveillance in the modern management of maternal diabetes mellitus, iatrogenic prematurity is at times required to prevent IUFD.[2,3]

IDMs appear to be at a particular risk for respiratory distress syndrome (RDS), even when they are not delivered prematurely.[105] This risk may be amplified by the fact that in poorly controlled diabetes, fetal hyperinsulinism causes a delay in surfactant production, placing the IDM at a higher risk of RDS than non-IDMs, at any given gestational age.[105,106] However, we demonstrated that adequate glycemic control reduces the risk of RDS to that of the nondiabetic population.[107] Moreover, we also have shown that with modern management and adequate prenatal care, IDM born very low birthweight do not seem to be at an excess risk of developing RDS or other major complications of prematurity compared with non-IDM.[108] Nevertheless, the presence of respiratory

distress in IDMs is not necessarily indicative of RDS. Indeed, such patients are at a higher risk for transient tachypnea of the newborn (TTN), probably due to a much higher rate of cesarean deliveries. Also, respiratory symptoms may be very well linked to the development of asymmetric septal hypertrophy (ASH), a kind of cardiomyopathy specific to hyperinsulinism, which leads to systolic left outflow obstruction.[109] Elevated cardiac troponin 1 concentration in IDMs with RDS appear to be excellent predictors of ASH.[110] This entity is best diagnosed by echocardiography and is particular because inotropic agents are specifically contraindicated in its management, as they may increase the strength of cardiac contractions and aggravate the left outflow obstruction.[109]

NEONATAL MANAGEMENT OF THE IDDM

Delivery Room Management

We believe that in view of the risk of significant dystocia and that of neonatal depression due to fetal acidemia, a team of professionals trained in the pediatric management of complicated deliveries should be present in the delivery room. This team may be composed of physicians, neonatal nurse practitioners, midwives, or respiratory therapists with formal training and experience in neonatal resuscitation. These professionals should apply all standards and techniques described in the Neonatal Resuscitation Program, program developed as a joint effort of the American Heart Association, and the American Academy of Pediatrics.[111]

Nursery Management

The IDM that required respiratory assistance at delivery should be evaluated and monitored at least in a level II or III facility. Otherwise, its management may be well conducted in a well baby nursery, provided that the following steps guidelines are addressed and facilities are available:

1. Vital signs examination and monitoring, including heart rate, respiratory rate, and blood pressure, at least hourly for the next four hours during which signs and symptoms of complications such as hypoglycemia or RDS may develop.
2. Complete physical examination by a trained physician as soon as possible after birth. The physical examination will be meticulous in searching for birth trauma (long bones, clavicular fractures, and peripheral neurological deficits), major and minor congenital malformations, and for the determination of the neurologic status of the infant that may have been affected by acid–base status, hypoglycemia, or polycythemia. The time at which meconium is first passed should be noted; SLCS is usually suspected when there is a delayed evacuation of meconium.
3. Screening for and management of neonatal hypoglycemia. We base the following recommendations upon those suggested by an expert committee who published on the topic.[66] Glucose monitoring should be initiated as soon as possible after birth, within two hours and before feeding, or at any time there are abnormal signs. Glucose reagent strips are commonly used in the newborn nurseries to screen for low blood glucose concentration. These methods should only be considered as a screen or an estimate because they may not be reliable and should not be used as the basis of a diagnosis.[66,112] At least one reliable laboratory value that is significantly low should be obtained when one considers the diagnosis of hypoglycemia in the newborn infant; however, awaiting laboratory confirmation should not delay treatment in a symptomatic infant. However, the final diagnosis should depend on the laboratory plasma glucose values. If the plasma glucose concentration is less than 36 mg/dL (2.0 mmol/L), a close surveillance should be maintained, and intervention is recommended if plasma glucose remains below this level, if the level does not increase after a feed, or if abnormal clinical signs develop. At very low glucose concentrations (<20–25 mg/dL, 1.1–1.4 mmol/L), intravenous (IV) glucose infusion aimed at raising the plasma glucose levels above 45 mg/dL (2.5 mmol/L) is indicated. This therapeutic objective (plasma glucose > 45 mg/dL, 2.5 mmol/L) is different from the operational threshold for intervention (36 mg/dL, <2.0 mmol/L). The higher therapeutic goal includes a significant margin of safety in the absence of any data evaluating the correlation between glucose levels in this range and long-term outcome in full-term infants.[66] As noted by Cornblath et al.,[66] the recommendation for maintaining therapeutic levels in excess of 60 mg/dL (3.3 mmol/L) may be indicated in the symptomatic infant with documented profound, recurrent, or persistent hyperinsulinemic hypoglycemia,[113] but it should not be the therapeutic goal for the majority of newborns with transient or brief episodes of low plasma glucose concentrations that are less than the operational thresholds recommended here.
4. Management of respiratory distress. The presence of respiratory distress in an IDM represents a particular challenge for the neonatologist. While respiratory distress may be indicative of congenital pneumonia, or spontaneous pneumothorax as in any other infant, the IDM may be more prone to TTN, due to a higher rate of cesarean deliveries, RDS, a higher rate of prematurity and delayed production of surfactant, and heart failure caused by ASH, than any other infant. The management of each condition is strikingly different. While all may require a similar symptomatic approach, such as administration of oxygen and ventilator support as needed, RDS may require administration of surfactant, ASH, the use of β-blockers,[114,115] and TTN only time to improve. Thus, for every IDM with respiratory distress, careful evaluation of the history and pattern of the respiratory distress is fundamental. Maternal fever in labor and prolonged rupture of membranes may point out to potential pneumonia or sepsis and justify the use of antibiotics; rapidly improving respiratory distress supports the diagnosis of TTN, while rapidly deteriorating distress may indicate the development of RDS or the presence of ASH. All IDMs with respiratory symptoms should undergo (1) an urgent chest X-ray, which may help distinguish between RDS, pneumonia, and TTN, or that will reveal another cause; and (2) an echocardiogram, to verify the presence or absence of an anatomic heart disease or ASH. If present, ASH should be managed with β-blockers (propranolol, starting oral dose: 0.25 mg/kg per dose Q6 hours, increased as needed to maximum of 3.5 mg/kg per dose Q6 hours; starting IV dose: 0.01 mg/kg Q6 hours over 10 minutes, increased as needed to maximum of 0.15 mg/kg per dose Q6 hours) only when symptomatic, and under careful monitoring of the blood pressure.[114,115]

5. Imaging. We do not advocate routine imaging studies for the screening of malformations. These studies were probably conducted, in most cases, prenatally (using ultrasonography), and the majority of malformations in the IDM should not be a "surprise" at the time of delivery. However, some malformations may not be detected by antenatal ultrasonography, such as a small ventriculoseptal defect; thus, we advise performing echocardiography only when signs or symptoms pointing to a possible cardiac problem are present. Similarly, the documentation of ASH, if asymptomatic, is relevant only from an academic standpoint.
6. Blood testing. We believe that a routine hematocrit value should be obtained, preferably from a venous sample, to screen for neonatal polycythemia at the time of peak hematocrit, that is at two to four hours of life.[56] Polycythemia (venous hematocrit ≥ 65%) should be treated by a dilutional exchange transfusion only if symptomatic, or if accompanied by significant or persistent hypoglycemia or if the venous hematocrit exceeds 70%.[116] Although the efficacy of dilutional exchange transfusion in preventing the late neurologic complications of polycythemia is controversial, we believe that in IDMs, it should be performed for the aforementioned indications because of the contribution of polycythemia to refractory hypoglycemia, and because of the high incidence of neurologic complications of polycythemia when hypoglycemia is concomitant.[117–118]

NHC and hypomagnesemia should be screened routinely at the age of 24 hours (i.e., at the nadir of postnatal values of serum calcium).[118] Due to the potential effect of NHC on the central nervous system and on the heart, there is little controversy on the need for treatment if there is symptomatic hypocalcemia with arrhythmia, pump failure, or seizures.[119] IV administration of Ca salts is the preferred, most rapid means of correction. Acute correction may be achieved by IV bolus infusion, over 10 minutes, with electrocardiographic monitoring of 18 mg elements Ca/Kg, followed by continuous infusion at 75 mg/kg/24 h.[120] Stepwise reduction of calcium dose over a period of 3 days usually prevents rebound hypocalcemia.[118] Calcium gluconate is usually preferred to Ca chloride, which may cause significant metabolic acidosis.[118] Continuous infusion is preferred to bolus, since the latter will acutely increase serum osmolality, decrease serum pH by competition of Ca++ with H+ at the bone,[118] be excreted in greater quantity,[118] and may depress parathyroid function.[118] In addition, boluses are more likely to cause arrhythmia, especially bradycardia, and possibly, cardiac standstill. Both bolus and continuous infusion of IV calcium may have the following complications: extravasation of calcium into soft tissue with Ca deposition or sloughing of the skin, and sometimes, severe cutaneous necrosis.[119,120] Intraarterial infusion is prohibited as organ necrosis such as intestinal necrosis[121] may result from it. In the cases where enteral Ca treatment is possible, a recognized side effect of enteral Ca salts is an increased frequency of bowel movement.[103]

In cases of refractory or relapsing hypocalcemia, it is advised to correct the often associated Mg deficiency. A single dose of 0.12 mL/kg of intramuscular 50% solution of magnesium sulfate (6 mg/kg of elemental magnesium) will, on average, increase within six hours the serum Mg concentration by 1 mg/dL, and correct the hypocalcemia.[118,119] Rarely is a repeat dose administered.

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Life Span Outcomes for the Child of the Diabetic Mother

10

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He who cures a disease may be the most skillful but he who prevents it is the safest physician.

—Thomas Fuller

Key Points

- Intrauterine environment can induce metabolic programing through epigenetic modification.
- Intrauterine exposure to maternal diabetes may have long-term effects on the developing fetus resulting in earlier onset of obesity and diabetes, cardiovascular abnormalities, and neurobehavioral problems.
- Early onset of obesity and diabetes may lead to a vicious cycle ofpre-gestational and gestational diabetes mellitus in the next generation.
- Health providers need to consider interventions in the critical "windows" of fetal programming such as pre-conception and during early pregnancy in order to decrease those long-term effects of maternal diabetes mellitus.

Pregnancy is a progressively hyperglycemic period which is necessary for the nutritional needs of the growing fetus.[1] However, diabetes in pregnancy is associated with an increased risk of fetal, neonatal, and long-term complications in the offspring.[2] This chapter summarizes the complications and outcomes seen in the offspring of the diabetic mother, starting from intrauterine developmental influences of hyperglycemia, "metabolic programming" and epigenetic modification in to future development of metabolic syndrome, diabetes mellitus (DM), obesity, and other long-term complications.

MATERNAL DM—SHORT-TERM NEONATAL COMPLICATIONS

Maternal DM may be gestational (diagnosed first during pregnancy) with a prevalence rate of about 7.5% or pre-gestational (i.e., type 1 and type 2 DM) with a prevalence rate of about 1.8%. The time the mother develops DM and the cell differentiation stage at this point will determine the kind and severity of complications,[3] and generally the outcome is related to the timing, duration and severity of glucose intolerance during pregnancy.

Pre-gestationaldiabetes mellitus (PGDM) leading to maternal hyperglycemia in the first trimester and time of conception, can affect organogenesis, resulting in diabetic embryopathy and major birth defects (i.e., open neural tube defect, transposition of great vessels, cardiac, renal, and gastrointestinal malformations). General mechanism to explain diabetic embryopathy may be impaired gene expression in the embryo, resulting from oxidative stress, and consequent apoptosis or disturbed organogenesis.[4,5] In contrast to PGDM, the development of gestational diabetes mellitus (GDM)is not known to be associated with an increased risk for teratogenesis[6,7] unless type 2 diabetes was previously undiagnosed.[7,8] Diabetic fetopathy, occurring in the second and third trimesters, results mainly in fetal hyperglycemia, hyperinsulinemia, and macrosomia.

UNDERLYING MECHANISM

Maternal serum glucose freely crosses the placenta, while maternal insulin does not. When a fetus is exposed to high levels of maternal glucose, its pancreas (although immature) responds by secreting high level of insulin into its circulation to control hyperglycemia which in turn, acts as a growth hormone and promotes fetal macrosomia and an increased rate of delivery complications.[9] Although the newborn is usually overweighed (macrosomic), in cases of severe diabetes, when nephropathy is present (class F), the offspring may also be small for gestational age (SGA).[10,11] Postpartum neonatal hypoglycemia may occur later due to continues neonatal production of insulin without further exposure to high levels of maternal glucose whichleads to a virtual neonatal hyperinsulinemia and subsequent hypoglycemia, requiring glucose infusion after delivery.[12,13]

RESISTANCE OR SECRETION?

Whether offspring displays reduced insulin secretion or heightened insulin resistance is not yet clear. While Silverman et al.[14] reported a high insulin:glucose ratio in response to oral glucose load, suggesting reduced insulin action, Pirkola et al.[15] and Plagemann et al.[16] showed no abnormality in children from mothers with GDM suggesting a small difference in the underlying mechanisms of PGDM and GDM.[9,17]

LONG-TERM EFFECT

It is well-established that GDM has long-term maternal consequences such as a significant risk for maternal type 2 DM. Recently, GDM was found to be an independent risk factor for long-term cardiovascular morbidity in a follow-up period of more than a decade.[18] In a retrospective population-based study on a cohort of women with and without a diagnosis of GDM, it was found that out of 47, 909 deliveries that met the inclusion criteria, 4928 (10.3%) occurred in patients with GDM. During a follow-up period (of more than a decade), after adjustment for age and ethnicity, patients with GDM had higher rates of cardiovascular morbidity including non-invasive cardiac diagnostic procedures (OR = 1.8; 95% CI 1.4–2.2), simple cardiovascular events (OR = 2.7; 95% CI 2.4–3.1), and total cardiovascular hospitalizations (OR = 2.3; 95% CI 2.0–2.5). Figure 10-1 presents a Kaplan-Meier analysis for the cumulative incidence of cardiovascular hospitalizations following the index birth in patients with and without GDM.

Likewise, there is growing evidence that maternal DM during gestation could result in subtle effects, which appear as health issues later in life including obesity, type 2 DM and post-natal neurobehavioral abnormalities in the offspring.[19,20] These effects usually are not seen immediately after birth and might have an important impact on the health of the individual during adulthood.

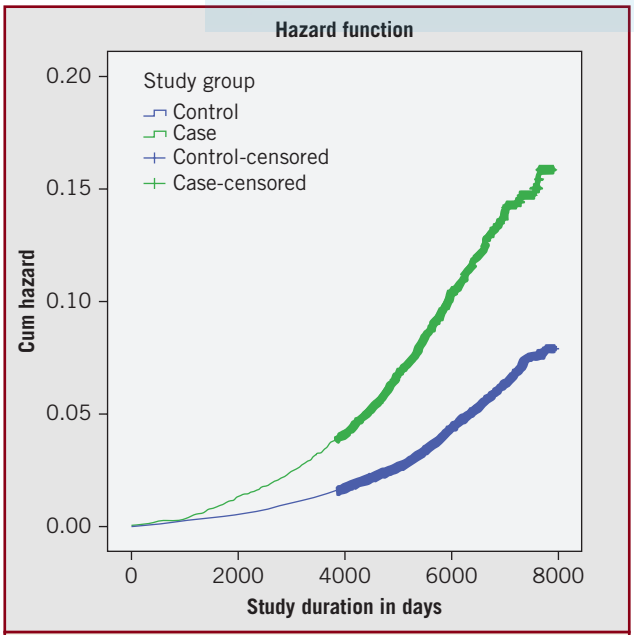

Figure 10-1 Kaplan-Meier Survival analysis curve (presenting hazard function) for cardiovascular morbidity of patients with and without a history of GDM.

THE CONCEPT OF INTRA-UTERINE AND EARLY LIFE METABOLIC PROGRAMMING

Epidemiological studies have raised the possibility that early lifestyle factors, which are not determined by the individual but rather by the intrauterine or neonatal environment, are critically important. A stimulus or an insult at a critical and sensitive period of time during development, especially when rapid cell division, differentiation and maturation are taking place, may lead to alteration of intrauterine and postnatal environment. Those alternations may be induced by nutritional, metabolic, and hormonal events[21] and may permanently alter the organism's physiology and metabolism. Accordingly, they might have long-lasting consequences on tissue or organ function by "*programming*."[11,22] This metabolic programming (also known to be designated as fetal programming[23] or metabolic imprinting[24]) may predispose the development of disorders and diseases later in life.

In the case of type 2 DM, elevated insulin concentrations, and less favorable early-life adaptations during critical periods of perinatal life may induce a long-lasting "malprogramming" of neuroendocrine systems (i.e., endocrine pancreas, and or insulin-sensitive target tissues) regulating body weight, food intake, and metabolism that persist into adult life and predispose to the development of obesity, DM, and consecutive risks.[22] This acquired disposition depends, at least in part, on the fetal insulin levels and perinatal hyperinsulinism and may occur even irrespective of the genetic background.[21]

FETAL EXPOSURE TO MATERNAL DM-DEVELOPMENT PLASTICITY

As mentioned above, there are critical periods in differentiation and maturation of the tissues and cells involved in organogenesis throughout gestation and early postnatal life. It should be emphasized that although organogenesis mostly related to the first half of pregnancy there are still some major developmental events that occur during the second half of pregnancy when GDM develops.

Nephrogenesis occurs during fetal life and stops after birth in humans.[25] Reduced numbers of nephrons at birth is a life-long deficit, as all nephrons are formed during a sensitive period of development during late gestation.[14] Maternal hyperglycemia may lead to developmentally induced deviations from the optimal ratio of body mass to nephron number[26] and alterations of insulin growth factor expression and their receptors in fetal kidney.[27] A relative deficiency in the number of nephrons is thought to increase the risk of inadequate renal function and hypertension in later life.[28,29] Ultimately, it could predispose renal failure and a potentially reduced life span.[30]

Echocardiography measurements of fetal cardiac left and right ventricular dimensions and contractility during the third trimester of in utero life, demonstrated *cardiovascular changes* in pregnancies complicated by diabetes. In relationship with the fetal

size both of the ventricular dimensions, the contractility and left ventricular output were decreased. These findings may reflect biochemical alterations in diabetic myocardiumand cardiovascular system that affect its function.[31] Manderson et al. suggested that exposure to a diabetic intrauterine environment during pregnancy is associated with an *increase in plasma concentrations of soluble adhesion molecules* in the diabetic offspring and significantly so for vascular adhesion molecule-1 (VCAM) and intercellular adhesion molecule-1 (ICAM), suggesting that inflammation could also be programmed by an adverse intrauterine environment. This may also be linked with development of cardiovascular disease later in life[2,31] as increased plasma concentrations of soluble adhesion molecules have been shown to predict cardiovascular disease in healthy men.[32]

Late gestation isalso critical for the nervous system development, proliferation and differentiation of *endocrine pancreas*.[33] During this period of time, fetal beta-cells respond readily to changes in the glucose and amino acid levels.[34] Therefore, an event occurring during the second half of pregnancy may lead to neuronal and beta-cell defects which will increase beta-cell apoptosis, reduce the growth of the endocrine pancreas, and eventually lead to hyperglycemia and impaired insulin secretion when the offspring will become adult. Because the vascular system is critical for normal organogenesis, *reduced angiogenesis* linked to hyperglycemia may also relate to reduced pancreatic growth as an additional mechanism.[11]

Diabetes during pregnancy accompanied by maternal hyperglycemia stimulates fetal insulin synthesis and increases amniotic-fluid insulin levelsand fetal adiposity, which may *permanently* influence fetal adipocyte mass.[35] *The hypothalamus* plays an essential role in the control of energy, and hypothalamic neuropeptides can be permanently altered by the maternal and fetal dietary environment.[36] Maternal hyperglycemia during pregnancy was thought to be one of the most important predictive factors of infant obesity and impaired glucose tolerance (IGT).[37,38] Recently, the neurotrophic role of insulin is emerging, showingthat elevated fetal insulin may affect its *hypothalamic development*.[39–41] Suboptimal or neonatal hyperinsulinemia may result in the malformation of hypothalamic structures and their role in the control of food intake. In animal model, dysplasia of the ventromedial hypothalamic nucleus, an area known to inhibit food intake and insulin secretion via sympathetic tone, was observed in offspring of gestational diabetic rats. This abnormality was long lasting and is suggested to be induced by fetal hyperinsulinemia in the perinatal period.[42] Further studies showed thatislet transplantation occurs before the last third of gestation and normalization of maternal glucose levels can be preventthis abnormality.[43,44]

Insulin is also an important mediator of the development of *hypothalamic circuits* and is responsible for changes in the innervations and neurotransmitter secretion of hypothalamic neurons as demonstratedin animal models.[45] Insulin in the brain decreases food intake and increases leptin secretion by adipocytes and placenta. When insulin resistance (or depletion) occurs, it may also promote hypothalamic resistance to leptin, elevated neuropeptide Y levels in the brain, and hyperphagia.[21] Those neuroendocrine effects on the fetal brain during critical windows of brain development are also found to be long lasting, affecting hypothalamic organization, and metabolism throughout adulthood.[21,41]

Many of the *major developmental events of the cerebral cortex* occur during the second half of pregnancy. Ornoy et al. found that children born to mothers with either GDM or PGDM have more difficulties in their gross and fine motor function as observed on developmental testas compared with controls.[10,19,36] There were also more children with an abnormally higher score on the questionnaires that screens for Attention Deficit Hyperactivity Disorder (ADHD).

THE ROLE OF EPIGENTIC REGULATION

Several studies were made in order to understand how do intrauterine growth disturbances remain as a stable memory in the later biology and behavior of the offspring. Early in 1975, Dorner et al. suggested the possibility of an epigenetic mode of diabetes transmission mediated by the mother.[46] Although classical theories of disease development assumed that genetic susceptibility is involved in a certain fraction of such transmission of vulnerabilities from mother to offspring and from intrauterine nutritional changes to postnatal growth and development, this new understanding of genome-function is emerging.[19] It suggests that epigenetic mechanisms are responsible for tissue-specific gene expression during differentiation and that these mechanisms underlie the processes of developmental plasticity.[47]

Epigenetic modifications in gene activity are taking place without a change in the nucleotide sequence. These modifications of the genomeare related to thetiming and expression of the genes and are being governed by a set of markings of the genome termed "epigenome."[19] This mechanism allows stable transfer of gene activity states from one generation of cells to the next. Examples for epigenetic mechanisms include DNA methylation, histone modification, and those of the microRNA machinery and it may be induced by the incidence of environmental factors such as hyperglycemia. Transcriptional factors,[48] insulin-secretion related genes,[49] glucokinase genes[50] or imprinted genes inherited from either the mother or father[51] are suggested to be influenced by intrauterine environment, making them good candidates for fetal programing.[11] These modifications mayresult in a long-term imprint on gene expression that lasts into adulthood[10,51,52] and it may affect biological systems, making them important pathogenic mechanisms in complex multifactorial diseases.

When malprogramming occurs in genes that are critical for development, it may result in teratogenicity or early neurodevelopmental deficits, whereas minor responses in the physiological range could increase the risk of development of neurobehavioral problems, obesity, and type 2 DM later in life.[10] Restoring aberrant phenotypes to normal is a great deal of research nowadays and it has led to promising speculation that, ultimately, susceptible people might be identified by means of screening for epigenetic markers during early life and that customized interventions might then be instituted.[47]

EPIDEMIOLOGICAL AND HUMAN STUDIES

The metabolic predictors of development of type 2 DM such asinsulin resistance and insulin secretion[53] and the long-term effects of a diabetic pregnancy on the offspring have been widely

investigated. Although a great deal of literature is derived from animal models using various methods, this section addresses human epidemiological and observational studies.

Future Development of DM in the Offspring

Dorner's original report over 35 years ago, suggested that susceptibility to DM could be acquired through transmission in utero from the mother to the child. He reported that adults with type 2 DM had a higher prevalence of type 2 DM on the maternal side compared with the paternal side.[46] Dorner's hypothesis has been supported in many observational studies since then, most studies relay on questionnaires and are retrospective, such as those of Thomas et al. and Alcolado and Alcolado who showed, in two cross-sectional epidemiological studies, that individuals with type 2 DM have approximately twice as many mothers (as compared with fathers) with DM.[54,55] Very high risk (with an OR of about 9) for abnormal glucose homeostasis (IGT or type 2 DM) among offspring with early onset maternal diabetes (<50 year old) was demonstrated in the Framingham prospective study and is consistent with the hypotheses of intrauterine exposure to diabetes as a risk factor.[56]

Most frequently cited aretwo major prospective studies, evaluating the long-term effects of diabetic pregnancy on the offspring, the Pima Indian Study and the Diabetes in Pregnancy Study at Northwestern University in Chicago which was composed of American mixed racial and ethnic population. Silverman et al. at the Northwestern Universitystudyevaluated long-term complication among offspring of diabetic mothers with both PGDM and GDM compared to unrelated children born to normoglycemic mothers.[14] Offspring of mothers with the highest amniotic fluid insulin concentrations in utero, as documented by measurement of the concentration of insulin in amniotic fluid at 32–38 weeks of gestation, had a remarkably high frequency of IGT by 10-16 years of age with characteristics of Type 2 DM, regardless of the mother's type of diabetes. On the contrary, offspring of diabetic mothers with normal amniotic fluid insulin concentrations had an incidence of IGT similar to that of the general population.

One of the most notable studies implyingmaternal transmission of type 2 DM was made on Pima Indiansfrom Southern Arizona, a population that suffers from high rates of obesity and the world's highest rate of type 2 DM.[57,58] Dabelea and Pettitt relied on true glucose measurements for over 30 years rather than on assessment of family history of DM.[59–61] Patients were divided in to 3 different groups: (1) offspring of women who had DM before or during pregnancy (diabetic mothers), (2) offspring of mothers who developed DM after pregnancy (pre-diabetic mothers), and (3) offspring of mothers who remained non-diabetic. Comparison between these groups after adjustment for paternal diabetes, age of onset of diabetes in father and mother and obesity in the offspring, showed that during childhood and early adolescence DM was particularlyfound in offspring of diabetic mothers. Later on, there was up to a six-fold higher prevalence of type 2 DM in those born to diabetic than to non-diabetic or pre-diabetic mothers. There was almost no difference in the prevalence of DM between offspring of pre-diabetic and non-diabetic mothers.[60] Figure 10-2 shows the age-specific prevalence of type 2 diabetes in the three subject groups (offspring of diabetic mothers, offspring of pre-diabetic mothers, and offspring of non-diabetic mothers).[62] In order to strengthen the role of exposure tothe diabetic intrauterine environment, the prevalence of type

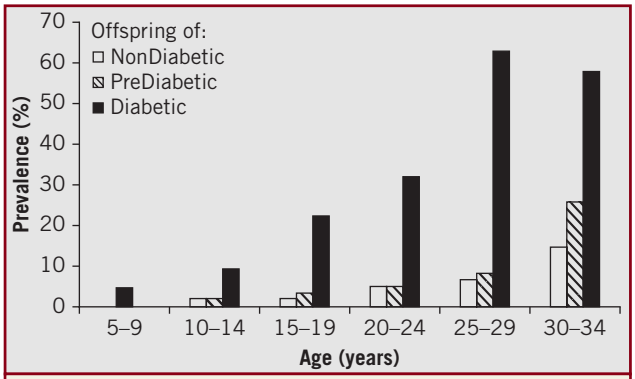

Figure 10-2 Prevalence of type 2 diabetes by mother's diabetes during and following pregnancy in 5-34-year-old Pima Indians. Copyright Taylor and Francis Journals (http://www.tandf.co.uk/journals). (Adapted from Dabelea D., Knowler W.C., Pettitt DJ, *The Journal of Maternal-FetalMedicine*, Vol 9, 2000 (6). Reprinted with permission from Taylor and Francis Journals.)

2 DM was compared in Pima Indian siblings born before and after their mother developed DM.[59,63] By that, genetic predisposition as a sole factor for Type 2 DM transmission was eliminated since siblings born before and after a diabetic pregnancy shared the same environmental and genetic susceptibility. Offspring born after their mother displayed DM had a significantly higher risk for developing diabetes than those born before the mother's diagnosis of diabetes (odds ratio 3.7, $P = 0.02$). In contrast, there were no significant differences in risk of diabetes between offspring born before and after the father was diagnosed with diabetes. Table 10-1 summarizes studies showing independent association between maternal hyperglycemia and offspring risk for type 2 DM. It should be emphasized, however, that several reports offer no evidence at all in support of independent association between maternal hyperglycemia and offspring risk for type 2 DM.[31,64–67] Table 10-2 summarizes studies that do not support the association between maternal hyperglycemia and offspring risk for type 2 DM.

Obesity

In 1983, Pettitt el al. suggested in the Pima Indian study that prenatal environment of the offspring of diabetic women results in the development of obesity in childhood and early adulthood. In this study, it was found that the offspring of diabetic mother were about twice as likely to be severely obese as compared to non-diabetic or pre-diabetic mothers and that at the age of 15–19 years, 58% of the offspring of diabetic mothers weighed 140% or more of their desirable weight, as compared with 17% of the offspring of non-diabetics and 25% of those of prediabetics.[68]

Figure 10-3 shows the age-specific prevalence of obesity in the three groups: offspring of diabetic mothers, offspring of pre-diabetic mothers and offspring of non-diabetic mothers.[62] Further studies have shown that offspring born after their mother displayed DM had a significantly higher (3.7-folds) mean body mass index (BMI).[59]

Those findings were supported by the Northwestern University study which also showed that amniotic fluid insulin concentration during 32–38 weeks of gestation may predict obesity during childhood.[14]

TABLE 10-1 Summary of Studiesin Favor of an Association Between Maternal Hyperglycemia and Offspring Risk for Type 2 Diabetes Mellitus

Method	Study	Year	Conclusions	P
Retrospective parental and offspring phenotypes	Dorner, et al.[46]	1975	Predominance on the maternal side as compared to the paternal.	<0.001
	Alcolado JC, Alcolado R.[54]	1991	Mothers were implicated in significantly more cases than fathers.	<0.001
	Thomas, et al.[55]	1994	Mothers were implicated two times more frequently than fathers.	<0.001
	Meigs, et al.[56]	2000	Maternal diabetes and an age of onset of <50 years had marked increased risk for both type 2 diabetes and abnormal glucose tolerance.	N/A
Prospective measurement ofamniotic fluid insulin at 32–38 weeks of gestation and postnatal glucose and insulin measurements	Silverman, et al.[14]	1995	Excessive insulin secretion in utero is a strong predictor of IGT in childhood.	<0.001
Longitudinal study comparing diabetes rates in offspring of pre– diabetic, non-diabetic and diabetic mothers during pregnancy	Pettitt, et al.[61]	1985	In all age-groups, there was significantly more diabetes in the offspring of diabetic women than in those of pre-diabetic and non-diabetic women	<0.05
Longitudinal study measuring the prevalence of diabetes in siblingsborn before and after their mother was recognized as having diabetes	Dabelea, et al.59	2000	The risk of diabetes was significantly higher in siblings born after the mother developed diabetes than in those born before the mother's diagnosis of diabetes.	0.02

TABLE 10-2 Summary of StudiesThat Do Not Support an Association Between Maternal Hyperglycemia and Offspring Risk for Type 2 Diabetes Mellitus

Method	Study	Year	Conclusions	PI
Retrospective parental and offspring phenotypes.	Viswanathan, et al.66	1996	No evidence for substantial maternal excess in the transmission of diabetes.	0.07
	Kim, et al.[64]	2004	Excess maternal transmission of type 2 diabetes was not observed.	0.104
Randomized control comparison of fasting blood measurements between type 1 diabetic offspring and controls.	Manderson, et al.31	2002	Fasting glucose and insulin did not differ between the offspring of diabetic mothers and control offspring.	>0.05
Prospective comparison of intravenous glucose tolerance test between offspring of type 1 and 2 diabetic women and controls.	Hunter, et al.65	2004	Intrauterine exposure to hyperglycemia by itself was not associated with alterations in glucose regulation in pre-pubertal offspring.	N/A
Comparison of young adult with a maternal history of pre-gestational diabetes to controls with no maternal history of diabetes.	Cross, et al.[63]	2008	Young adult offspring of mothers with pre-gestational diabetes do not differ in terms of glucose tolerance.	N/A

Blood Pressure and Cardiovascular Risks

Recently, the Pima Indian investigators have shown evidence for an association between maternal hyperglycemia and significantly higher systolic blood pressure emerging during childhood.[69] This association confers an additional independent risk for the development of cardiovascular diseases later in life. Such risk was also demonstrated in the Diabetes in Pregnancy follow-up study at Northwestern University which found significantly higher systolic and mean arterial blood pressure in offspring of diabetic mothers.[70]

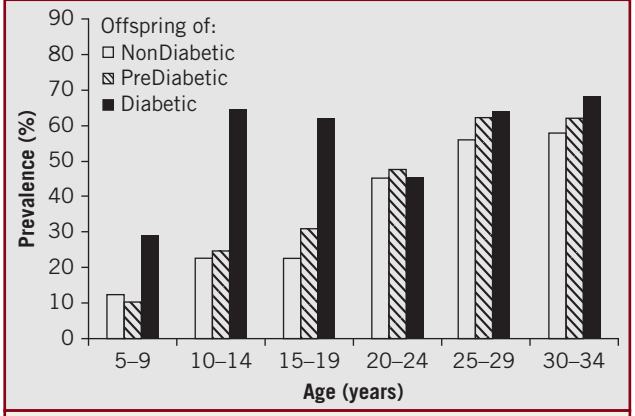

Figure 10-3 Prevalence of severe obesity (weight = 140% of age-sex-height specific standard) by mother's diabetes during and following pregnancy in 5-34-year-old Pima Indians. (Copyright Taylor and Francis Journals (http://www.tandf.co.uk/journals). Adapted from Dabelea D., Knowler W.C., Pettitt D.J. *The Journal of Maternal-Fetal Medicine*, Vol 9,2000 (6). Reprinted with permission from Taylor and Francis Journals.)

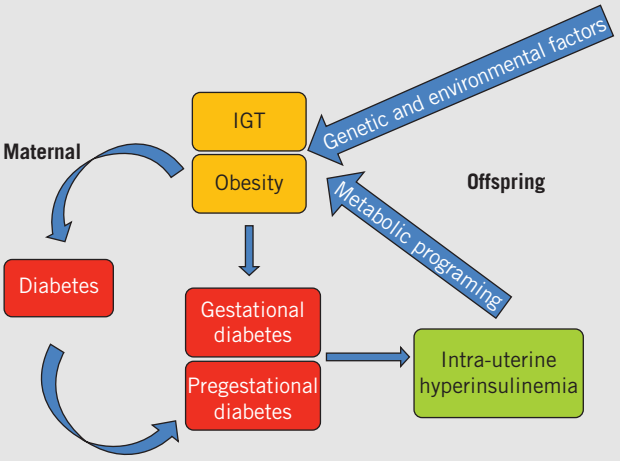

Figure 10-4 The possible role of intra-uterine hyperinsulinemia and metabolic programing as a consequent of maternal diabetes mellitus.

LEVELS OF MATERNAL HYPERGLYCEMIA AND THE LONG-TERM EFFECT OF TREATMENT

While levels of maternal fasting serum glucose concentration at diagnosis of GDM was a useful predictor for the risk of major anomalies,[71] there has been little attempt to address the relationship between the degree ofmaternal hyperglycemia and the incidence of diabetes in offspring.[12]

Hillier et al. suggested a relationship between hyperglycemia levels in GDM and increased future risk of obesity in children at age 5–7 years. His group also suggested that this risk is modifiable by treating GDM, as obesity risk was attenuated and no longer significant in the treated GDM group.[72] Clausen et al. followed 597 offspring of diabetic mothers at 22 years of age and compared them with a background population. They found that the degree of maternal hyperglycemia in the third trimester in type 1 diabetic mothers was a significant predictorof the child's glucose tolerance.[73]

So far there are no randomized control trials in which diabetic mothers were treated during pregnancy and offspring were followed up for future glucose intolerance.[12] Crowther et al.[6] and Landon et al.[74] demonstrated improved pregnancy outcome in the intensively treated groups compared to women with standard care treatment, implying a possible lower incidence of type 2 DM in offspring of intensively treated women. Future demonstration of this possibilitycould provide convincing evidence for the hypothesis of maternal transmission of type 2 DM.[12]

TYPE 1 DM, TYPE 2 DM, OR MAYBE GDM?

There appears to be a higher incidence of type 2 DM in offspring of women with type 1 DM, type 2 DM or with GDM and it seems like the type of maternal diabetes may be irrelevant to the relationship between maternal hyperglycemia and offspring diabetes.[16,38,72]

SUMMARY

Type 2 DM is increasing in epidemic proportions worldwide along with the tendency to develop DM at a younger age. This fact ultimately leads to epidemic range of GDM.[11] Apart from the immediate effects of intrauterine exposure to maternal DM (i.e. macrosomia, birth defects) it may have long-term effects on the developing fetus resulting in cardiovascular abnormalities, neurobehavioral problems, earlier onset of obesity, and diabetes leading toa vicious cycle of PGDM and GDM in the next generation (Figure 10-4.)

On the metabolic and molecular level, intrauterine environment can induce metabolic programing through epigenetic modification. Intrauterine programing may permanently alter the expression of genes and therefore the structure and function of the developing systems (i.e., defect in pancreas morphology and function, defects of angiogenesis, hyperinsulinism).

The predisposing effect of intrauterine exposure to a diabetic environment has major public health implications such as the concernthat the current practice of diagnosing gestational hyperglycemia in late pregnancy might be just too late. We should not ignore the long-term outcomes that might contribute to diabetes pandemic. It seems that health providers will need to concentrate on the health of young women and consider interventions in critical "windows" of fetal programming such as pre-conception and during early pregnancy, in order to break this vicious cycle and decrease those long-term effects of maternal DM.

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PART II General Clinical Management of the Pregnant Diabetic

Glucose Monitoring in Pregnancy Compromised by Diabetes

11

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Start with the end in mind.

—Stephen Covey

Key Points

- Intensified management and achievement of established levels of glycemic control using memory-based self-monitoring blood glucose (MSMBG) is associated with enhanced pregnancy outcome.
- The optimal frequency of blood glucose testing in patients with diabetic pregnancy has not been established.
- A single measure of glycemic level such as glycosylated hemoglobin has a marginal role in pregnancy since it is a poor predictor of pregnancy outcome.
- Continuous glucose monitoring (CGM) is effective in assessing the glycemic profile and may in the future facilitate treatment adjustment.
- The efficacy of using CGM in comparison to MSMBG for improved pregnancy outcome has not yet been established.
- New measures for glucose monitoring (i.e., glucose variability) should be studied in pregnancy.

INTRODUCTION

The ability to monitor glucose values is of historical significance, since throughout recorded history, physicians have been familiar with diabetes and have "finger-dipped" in order to detect the "sweetness" of patients' urine. This imperfect technique was used until the development of urine sticks in the early 20th century that were sensitive enough to detect glucosuria. Because of the increased glomerular filtration rate in pregnancy, the time interval over which urine accumulates in the bladder and the effect of the diabetic treatment on the glucose concentration, urine testing should never be used to evaluate levels of glycemic control in pregnancy.

Research efforts have continuously been directed towards the development of a process for testing blood glucose using either visual or electronic interpretation with a reflectance meter. The method of testing that was developed was based on obtaining a sample of capillary blood with specially designed lancets and placing it on a test strip composed of glucose oxidase and peroxidase. The strips were visually read, went through a color change, and matched against a color chart that provided blood glucose ranges but not specific glucose values.

In the late 20th century, it became technically achievable to test blood glucose values using reflectance meters. The original meters used a wet method that often required as many as four steps (approximately 10 minutes/step) to obtain one test result. Today's reflectance meters are more user friendly, include a memory chip for data storage and 1-step testing. This latest technological advancement made it possible for patients to monitor and test blood glucose values independent of care providers. The goal of achieving desired levels of glucose became a patient-care provider initiative. Recently, a continuous glucose monitoring technique was developed that facilitates the collection of even more accurate glucose data. In this chapter, the implications of using different methods to monitor glucose in the pregnancy compromised by diabetes will be addressed.

A SINGLE MEASURE OF GLYCEMIC LEVEL: GLYCOSYLATED HEMOGLOBIN AND GLYCOSYLATED PROTEIN

Traditionally, in nonpregnant diabetic patients, glycosylated hemoglobin (HbA_1C) became the indicator of long-term glycemia. HbA_1C is a modification of hemoglobin caused by the attachment of glucose to the N-terminus of the beta chain. The rate of attachment is determined by the glucose concentration in the blood. Based on the lifespan of the red blood cells which averages 120

days, different reports have suggested that the predictability of HbA_1C ranges from 4 to 10 weeks.[1–3] In pregnancy,[4,5] glycosylated hemoglobin does not correlate well with glycemic profile. This is especially true in gestational diabetic patients whose blood glucose is mildly elevated in comparison to type 1 and type 2 diabetes patients. Studies have reported no to moderate correlations between HbA_1C and different components of the glucose profile when an HbA_1C result of 4%–5% includes a capillary blood glucose range of 50–160 mg/dL (Table 11-1). There are several explanations that can address this variability. HbA_1C is a "continuous" measure while memory-based self-monitoring blood glucose (MSMBG) is a random sampling technique. The different turnovers of HbA_1C in pregnancy may affect its relation to mean blood glucose in comparison to the nonpregnant state. The weight of each glucose value is most probably unequal in terms of its impact on HbA_1C.

A second single measure is either glycosylated protein or fructosamine. Both have shorter life spans (7–10 days) and, therefore, may be used as a measure for short-term glucose profile evaluation. However, in pregnancy, a wide variability was found when they were compared to MSMBG and, to date, their role in evaluation of level of glycemia has not yet been established.

At best, these methods are retrospective measures that provide information for an indeterminate period (1–10 weeks) prior to the assay results. Thus, it is virtually impossible to alter treatment modality based on retrospective data, especially since the window of opportunity in pregnancy is so small. Lately, Jovanovic et al.[6] found that in 24 women with gestational diabetes mellitus (GDM) and initial $HbA_1C \geq 7.0\%$ a decline of 0.47% per week in HbA_1C levels was observed in response to carbohydrate-restricted diet or insulin treatment. This finding, if proven by larger scale studies, could reflect a possible utility of HbA_1C measurement during therapy. Until then, the notion that HbA_1C can be used for alteration of treatment algorithm in pregnancy must be seriously questioned. The only time HbA_1C should be used in pregnancy is for pre-existing diabetes especially at the first office visit for counseling for the risk of congenital anomalies and macro and micro complications throughout pregnancy.

Another potential marker for glycemic status is glycated albumin (GA), which reflects the status of glycemic control over a period of two to three weeks—the life span of albumin. Its measurement method is convenient, unaffected by albumin concentration and does not necessitate fasting.[7] In addition, as opposed to HbA_1C, GA is not affected by variant hemoglobin and some diseases that shorten the lifespan of erythrocytes, such as hemolytic anemia and renal anemia.[8] GA levels usually decrease in the third trimester in normal pregnancy and are affected by maternal obesity and the presence of proteinuria.[9] Recently, GA, has been shown to be correlated with the level of HbA_1C, preprandial, postprandial, and mean plasma glucose in gravida with GDM and diabetes mellitus in the second trimester.[10] Moreover, in a study[11] of 713 pregnant women with abnormal 50 g challenge test undergoing 100 g oral glucose tolerance test compared with HbA_1C, GA was more closely correlated with fasting and 120 minutes glucose, regardless of insulin resistance and blood pressure. However, further research is warranted in order to assess the correlation between GA levels and adverse outcome and whether intervention could positively affect it.

THE VALUE OF GLUCOSE MONITORING IN PREGNANCY COMPLICATED WITH DIABETES

Approximately 6%–15% of pregnancies in the United States are complicated by diabetes mellitus with 80%–85% of the cases represent women with GDM.[12,13] The actual prevalence, however, may differ with ethnicity and maternal age.[14] Women with elevated blood glucose levels experience a greater risk for adverse maternal and fetal outcomes,[15,16] including preeclampsia,[16,17] cesarean delivery,[18] and increased risk for future development of type 2 diabetes[19] and cardiovascular morbidity.[20] A common complication associated with GDM is fetal macrosomia,[21,22] which is associated with birth injuries and asphyxia.

It has been clearly demonstrated that intensified management and the achievement of established levels of glycemic control using MSMBG, glyburide treatment or if needed multiple injections of insulin, diet, and an interdisciplinary team effort was associated with enhanced pregnancy outcome.[23–25] The above recommendations support the routine use of MSMBG in the management of the pregnancy compromised by diabetes.

TABLE 11-1 The Association Between Glycosylated Hemoglobin and Verified Blood Glucose Data

	Nonpregnant		Pregnant			
	Type 1		Pre-Gestational		Gestational	
	r	*P*	*r*	*P*	*r*	*P*
Mean SMBG	0.55	<0.01	0.60	<0.03	0.51	<0.001
Fasting BG	0.80	<0.01	0.67	<0.03	0.52	<0.001
Pre-meal	0.71	<0.01	ns	ns	0.52	<0.001
Post-meal	ns	ns	ns	ns	0.51	<0.001
Bedtime	ns	ns	0.83	<0.001	ns	ns

IS THERE AN OPTIMAL FREQUENCY FOR BLOOD GLUCOSE DETERMINATIONS?

In a prospective study, Langer et al.[23] demonstrated that a mean blood glucose obtained from MSMBG (seven times daily) using memory reflectance meters, identified more fetal macrosomia and other neonatal morbidities in comparison to weekly fasting and two-hour laboratory glucose determinations supplemented by four times daily (unverified) self-monitoring with only test strips and no meters. Although women in the intensively treated group were asked to monitor self blood glucose levels seven times daily, compliance was not always ideal and they actually tested on average 5.2 per day. Others have reported similar results with four/day glucose determinations.[26,27] In patients with type1 diabetes, Kerssen et al.[28] compared the results of self-monitoring blood glucose (SMBG) and CGM. They found that the detection of hyper- and hypoglycemia was significantly higher in patients with 10 or more SMBG determinations daily than in patients with less than 10. The correlation of their finding with pregnancy outcome was not reported. Wechter et al.[29] evaluated the effect of diet (1800–2000 kcal) therapy and home glucose monitoring on neonatal macrosomia rates in 153 GDM women. Pregnancy outcome was compared to non-diabetic controls. Patients were instructed to test their blood glucose at fasting and two hours postprandial, three to five times per week initially and weekly thereafter. No significant difference was found in regard to either mean birth weight or the incidence of macrosomia between the two groups, which led the investigators to conclude that a program of intensive dietary therapy and home glucose monitoring, with therapeutic insulin as indicated, could reduce the incidence of macrosomia in gestational diabetes to that observed in the general population. Homko et al.[30] randomly assigned 58 women with diet-controlled GDM and a fasting blood glucose level <95 mg/dL to either four times daily glucose monitoring using a reflectance meter with memory periodic monitoring at prenatal visits. There were no significant differences with regard to dietary compliance, birth weight, gestational age at delivery, Apgar scores, and neonatal complications. Rates of macrosomia, delivery by cesarean section, and occurrence of birth trauma were similar.

Despite the fact that no consensus was reached, the optimal frequency for blood glucose monitoring should probably be different among the various diabetes groups with diet-controlled GDM needing the less frequent monitoring. Based on data available, the recommendation of the American Colleague of Obstetrics and Gynecology as recently published[31] are four times daily glucose monitoring preformed as fasting and either one or two hours after each meal with possible modifications made in diet-controlled GDM patients after reaching well-controlled glucose levels.

Introducing intensified therapy to newly diagnosed GDM women was questioned as potentially enhancing patient anxiety. It has been demonstrated that not only that intensified management of newly diagnosed GDM does not increase patient anxiety and depression, but also achievement of glycemic control contributes to patient reassurance. Psychological adjustment to the temporary disease state is then equal to that of a non-diabetic individual.[32]

MEASURING GLYCEMIA: FROM MSMBG TO MEMORY-BASED REFLECTANCE METERS

The role of MSMBG in intensified therapy in nonpregnant and pregnant women has become the standard to achieve targeted levels of glycemic control. On the other hand, MSMBG may have some disadvantages. It is painful to perform. Another shortcoming in the use of reflectance meters is that each glucose determination represents a sole glucose value during the day, a "snap shot" of glucose value. However, the four or seven daily determinations are performed to evaluate the pre- and postprandial glucose values and adjustment of insulin therapy when indicated.

When MSMBG is performed without memory reflectance meters to ascertain accurate and reliable verified data, the validity of the test results is questionable. It has been shown that in nonpregnant[33,34] and in the pregnant state[35] patients alters their blood glucose testing results. Langer and Mazze[35] demonstrated marked inconsistency between self-reported and actual blood glucose data from gravid diabetic patients. Thirty-four women were followed prospectively. They used reflectance meters, modified with the insertion of a memory microchip. Patients were blinded to the existence of the chip. The self-reported blood glucose results from patient logbooks were subsequently compared to values recorded by the memory chip in the reflectance monitor. In approximately 80% of the patients, a significant difference was demonstrated between logbook and memory meter results. The same authors[36] undertook a follow-up study to determine whether patients' awareness of a microchip in the reflectance monitor would improve the accuracy of the subjective reporting of self-monitoring data. They demonstrated a significant improvement in patients' compliance and reliability. Verified blood glucose collection would appear to enhance the accuracy and consistency of self-monitored blood glucose determinations. Currently, the majority of reflectance meters contain a memory chip to overcome the lack of compliance.

The memory reflectance meter led to the development of a novel approach to glucose data analysis, the ambulatory glucose profile by Mazze et al.[36] The Ambulatory Glucose Profiles (AGP) aggregate two or more weeks of glucose data into a typical 24-hour profile of continuous glucose data. The AGP provides information on glucose excursion, interquartile range (variability), stability (number of reversals from the median), and mean blood glucose. This allows patient glucose profile analysis beyond the mean. Langer et al.[37,38] demonstrated the similarity of the AGP between GDM women with two or more abnormal values on the OGTT results and women with one abnormal value. They also demonstrated the AGP of normal non-diabetic pregnant women and the profile of GDM women at different levels of glycemic control.

THE ROLE OF CONTINUOUS GLUCOSE MONITORING

Recently, several companies have attempted to develop a new technology that measures continuous glucose. Some of these techniques are non-invasive while others are minimally invasive.[39] Glucose monitoring methods employ four different approaches: transdermal, glucose electrode, micro-dialysis or open-flow micro-perfusion. Currently, two are commercially available. The

transdermal approach (Glucowatch; Cygnus, CA, USA) employs reverse iontophoresis by applying low voltage current to the skin surface causing interstitial fluid (containing glucose) to pass through the skin. Glucose is then measured by an oxidase reaction. This data also contains information about skin temperature and sweat that are all included in the calculation process.[40] The MiniMed CGM System (Sylmar, CA, USA) is composed of a disposable subcutaneous glucose-sensing device and an electrode impregnated with glucose oxidase connected by a cable to a lightweight monitor which is worn over clothing or a belt. The system measures glucose levels every 10 seconds, based on the electrochemical detection of glucose by its reaction with glucose oxidase, and stores an average value every five minutes, for a total of 288 measurements per day. The glucose measurement is performed in subcutaneous tissue in which the interstitial glucose levels are in the range of 40–400 mg/dL. The data are stored in the monitor for later downloading and reviewing on a personal computer. The patients are unaware of the results of the sensor measurements during the monitoring period. Glucose values obtained with CGM have been shown to correlate with laboratory measurements of plasma glucose levels[41] and with home glucose meter values.[42] To corroborate CGM system accuracy, patients are expected to perform three to five capillary blood tests daily using conventional meters. This additional chore becomes a potential burden for the patient. Pregnancy outcome is the only means to judge if having been subjected to CGM had been justified knowing a priori that MSMBG monitoring performs equally well.

The continuous glucose monitoring has been studied[43] in the nonpregnant population where it has facilitated the detection of previously unrecognized postprandial hyperglycemia and nocturnal hypoglycemia. In pregnancy, it was validated as an accurate tool for glucose monitoring especially in the women with preexisting diabetes mellitus.[44,45]

However, there are only limited randomized clinical trials assessing the usefulness of CGM in reducing the rate of diabetes-related pregnancy complications with conflicting results.[46,47] Murphy et al.[46] showed in 71 pregnant women with type 1 and 2 diabetes mellitus that intermittent (four to six weeks interval) CGM resulted in a significant reduction of HbA_1C at 32–36 weeks of gestation, lower birth weight, and reduced risk of macrosomia (odds ratio 0.36, 95% confidence interval 0.13–0.98, $P<0.05$) compared to standard antenatal care. In contrast, a recently published study[47] of 154 pregnant women with preexisting diabetes mellitus randomized to either real time CGM for six days at 8, 12, 21, 27, and 33 weeks of gestation or routine care only showed neither an improvement in glycemic control, reflected in similar rates of hypoglycemia events and HbA_1C levels, nor a reduction of large for gestational age neonates rate in the CGM group. Perhaps, the results of the GlucoMOMS trial,[48] a large multicenter randomized clinical trial ongoing in the Netherlands would clarify whether CGM use during pregnancy improves pregnancy outcome.

GLUCOSE MONITORING IN NON-DIABETIC PREGNANCY: WHAT IS NORMAL?

The goal of management in pregnancy complicated with diabetes is to maintain blood glucose as near to normal as possible. Until a decade ago, limited data existed concerning the normal glycemic profile in non-diabetic pregnancies.[49–51] Moreover, these studies included small sample sizes in a hospital environment, under strict diet limitations and data included only a single day of evaluation during the third trimester. In Addition, no stratification was performed for obesity.

However, since the widespread use of CGM in diabetes patient data regarding glucose levels in non-diabetic gravida was beginning to establish. Yogev et al.[17] analyzed three days of continuous glucose monitoring in non-diabetic gravid patients. During the study period, all women were asked to refrain from lifestyle modification or dietary restrictions. Significant differences in glucose profiles were established between obese and non-obese women. Moreover, the currently recommended clinical thresholds were found to be higher than this characterization of normoglycemia in non-diabetic women (Table 11-2). Siegmund et al.[52] described the first detailed longitudinal CGM profiles of healthy pregnant women ($n = 32$, mean age 29.6 ± 4.5 years, mean pre-pregnancy BMI 22.4 ± 2.5 kg/m^2) using 72 hour of retrospective CGM data obtained at 16, 22, 30, and 36 weeks gestation and repeated at six weeks post-partum. They documented the corresponding caloric

TABLE 11-2 Glycemic Profile in Non-Diabetic Gravid Women in Comparison to the Accepted Glycemic Threshold for Managing Pregnancy Complicated With Diabetes

	Recommended Glycemic Thresholds			Glycemic Profile in Non-Diabetic
	ACOG[31]	ADA[82]	Fifth International[83]	Yogev et al.[17]
Fasting (mg/dL)[a]	60–90	<105	<95	75 + 12
Pre meal (mg/dL)[a]	60–105	–	–	78 + 11
Post meal (mg/dL)[a]				
One h	<130–140	<155	<140	97.0 + 11
Two h	<120	<130	<120	105 + 13
90–120 min	–	–	–	–
2 am–6 am (mg/dL)[a]	60–90	–	–	68.3 + 10
Mean (mg/dL)[a]	100	–	–	84.0 + 18

intake using detailed food diaries (mean 2223 ± 356 kcal) which did not significantly change during pregnancy. Although fasting blood glucose levels did not change during pregnancy, a higher fasting postpartum level was (90.3 ± 10.8 mg/dL; $P = 0.00$) noted. The postprandial glucose levels rose from 95.4 ± 10.8 mg/dL at 16 weeks to 110.5 ± 12.6 mg/dL at 36 weeks, falling to 100.6 ± 10.8 mg/dL at six weeks postpartum. The mean CGM glucose values rose significantly, only during the third trimester (87.1 ± 7.2 mg/dL at 30 weeks to 93.9 ± 9.0 mg/dL at 36 weeks; $P = 0.002$), remaining unchanged at six weeks postpartum (93.6 ± 9.0 mg/dL; $P = 0.51$). This study demonstrated that postprandial glucose levels tend to rise as the pregnancy progresses even in normal healthy pregnancy with similar carbohydrate intake. Similar results using SMBG were reported previously.[53] Recently,[54] glycemia was prospectively measured in early (15.7 ± 2.0 weeks' gestation) and late (27.7 ± 1.7 weeks' gestation) pregnancy in normal-weight ($n = 22$) and obese ($n = 16$) pregnant women without diabetes on a controlled diet using 24-h CGM. The 24-h glucose area under the curve and nearly all fasting and postprandial glycemic parameters were higher in the obese women. Finally, when comparing glycemic profile between pregnant and nonpregnant state, a recent study by Mazze et al.[55] using three days of CGM found that diurnal glucose patterns differ throughout the day by 20% in women without diabetes mellitus.

THE POSTPRANDIAL GLUCOSE PROFILE IN THE DIABETIC PREGNANCY

Traditionally, in the management of diabetes complicating pregnancy, various methods of glucose monitoring have been proposed, including the measurement of fasting, preprandial, postprandial, and mean 24-hour blood glucose concentrations.[23,56–58] Several authors have emphasized the importance of postprandial glucose determinations and pregnancy outcome.[26,59] However, controversy exists regarding the timing for the use of one- or two-hour postprandial determinations and what is the appropriate threshold (<140 mg/dL in one-hour and <120 mg/dL two-hour postprandial) to define normality[26,59–61] as these thresholds are higher than the postprandial characteristics found in non-diabetic subjects (Table 11-2).

Therefore, should the postprandial threshold be modified in diabetic patients? Or, should the targeted postprandial values in pregnant diabetic women remain higher than the postprandial values found in non-diabetic women? By using CGM recording in 62 diabetic patients, we were able to analyze the first 180 minutes of each meal during the study period. We demonstrated[62] that the time interval from meal to peak postprandial glucose levels (approximately 90 minutes) was similar in all the evaluated types of diabetic pregnancies (type-1, GDM insulin treated or diet only) and is not affected by the level of glycemic control. Moreover, no difference was obtained in postprandial glycemic profile between breakfast, lunch, or dinner. Similar meal to postprandial peak interval was later reported by Bühling et al.[63] with no different results in diabetic and non-diabetic gravida. We recognize that future studies should look for the association between postprandial glucose values at 90 minutes and pregnancy outcome prior to recommending 90 minutes as the proper time for postprandial glucose analysis.

USING CGM FOR TREATMENT ASSESSMENT

The wide range of glucose values obtained with the use of the CGM provides the opportunity to identify both unrecognized hyperglycemia and hypoglycemic events in comparison to MSMBG.

Undetected Hyperglycemia

In pregnancies complicated with type 1 diabetes, we demonstrated[64] a mean total time (192 ± 28 min/d) of undetected hyperglycemia (glucose levels > 140 mg/dL) identified by CGM. The approximate three-hour hyperglycemia recorded throughout the day would not be recognized if MSMBG was used alone (Figure 11-1). Furthermore, when GDM patients were evaluated[65] the mean total time of hyperglycemia was 132 ± 31 min/d for insulin treated GDM and 94 ± 23 min/d for GDM patients treated with diet only. One possibility that macrosomia has persisted despite intensified care protocols is hyperglycemia events, often related to unscheduled meals, that were missed using SMBG protocols. Furthermore, these elevations of blood glucose often occurred shortly after patients took fasting and postprandial fingerstick glucose determinations that indicated that their glucose levels were in the target ranges. Importantly, no correlation was found between higher levels of HbA_1c and hyperglycemic episodes, another finding supporting the weak association between HbA_1c and glucose level monitoring in pregnancy.

Undetected Hypoglycemia

Despite years of meticulous study, there is still paucity of information regarding the optimal level of glycemia in diabetic pregnancy that clinicians should target to safely reduce maternal and perinatal morbidity. Strict metabolic control in this patient population has been associated with an increased risk of maternal hypoglycemia. Rosenn et al.[66] reported significant hypoglycemia, defined as hypoglycemia requiring assistance from another person, in 71% of gravid patients with type 1 diabetes with a peak incidence in the first trimester. In our study, using CGM, in type 1 gravid patients, hypoglycemic events were recorded in 76% of the patients, most of the episodes were nocturnal, some of them asymptomatic.[64] Interestingly, in all cases, an interval of one to four hours preceded clinical manifestations (Figure 11-2). When GDM patients were assessed, hypoglycemic events were recorded in 58% of the patients, all of them were insulin treated.[65]

In order to estimate the prevalence of undiagnosed, asymptomatic hypoglycemic events that occur in diabetic patients and to evaluate whether the rate of asymptomatic hypoglycemic episodes vary under different modalities of treatment for gestational diabetes, we conducted[67] a study using CGM on GDM patients treated with glyburide, insulin, or diet only. Asymptomatic hypoglycemic events were found to be common during pharmacological treatment in GDM. However, patients treated with glyburide had significantly fewer asymptomatic hypoglycemic events than insulin-treated patients. Patients treated with diet alone and in non-diabetic women, no hypoglycemic events were identified. Our findings may be explained by treatment modality as the side effect of pharmacological glycemic control during pregnancy rather than by the pathogenesis of the disease.

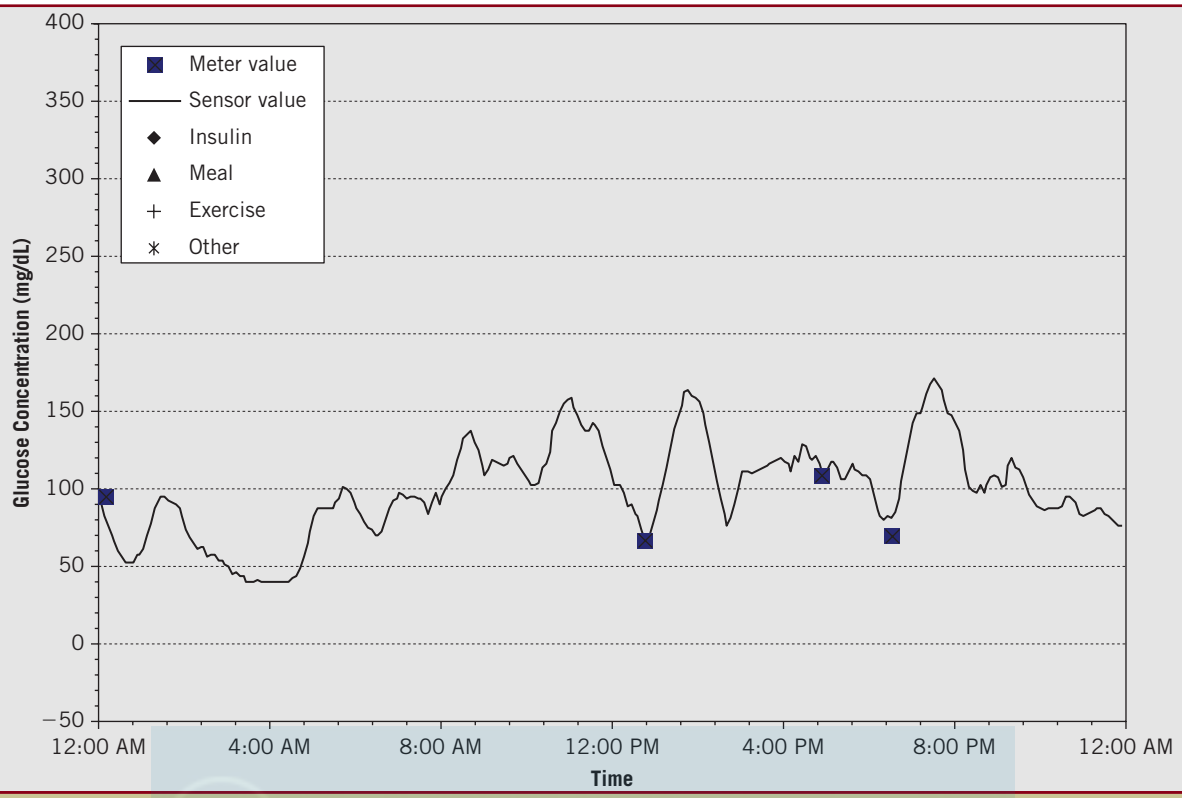

Figure 11.1 A 24-hour continuous glucose monitoring of type 1 patients at 32 weeks' gestation. There are three periods during the day with blood glucose >140 mg/dL detected only by CGM.

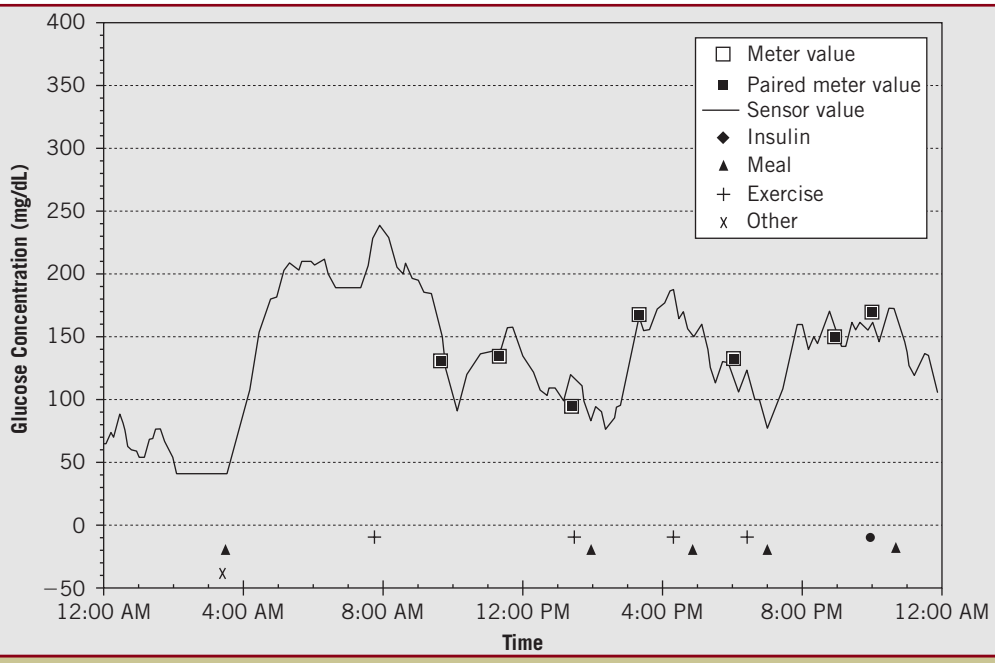

Figure 11.2 Nocturnal hypoglycemia in type 1 patients at 31 weeks' gestation. Note the three-hour interval prior to patient awareness.

CAN CGM BE USED FOR TREATMENT ADJUSTMENT?

We studied[68] eight women with diabetes in pregnancy, of whom six were type 1 and 2 were GDM. Data derived from the CGM for 72 hours were assessed and treatment was adjusted on the basis of the findings. Two to four weeks later, the patients were re-evaluated with CGM. In the second time, a significant reduction in mean blood glucose, hypoglycemic events and duration of undetected hyperglycemia was demonstrated. Moreover, we found[64] that in 70% (24/34) of pregnant women with type 1 diabetes insulin dose adjustment was necessitated due to CGM use. In a randomized trial Kestila et al.[69] reported 31% need for antihyperglycemic drug therapy in GDM women using CGM compared to only 8% of those using SMBG ($P = 0.0149$). In contrast, Kerssen et al.[70] reported that since there is a wide variability in the day-to-day glucose levels of pregnant women with type 1 diabetes, the use of CGM raises a problem for adjustment of therapy. They concluded that fine-tuning of insulin regimens based on three-day measurements with the CGM method is not advisable.

THE ROLE OF GLUCOSE VARIABILITY FOR GLYCEMIC MONITORING

Various methodologies have been proposed for analysis of continuous glucose measurements. Glucose variability is a method taking into account not only the standard points of interest (e.g., fasting and postprandial) but also the entire measurement's profile and especially the fluctuations in glucose level during the tested period. There is no one parameter to define glucose variability but rather several ones, which usually correlate with each other. Mean amplitude of glucose excursions (MAGE), total SD (SDT), the interquartile range (IQR), and the continuous overlapping net glycemic action (CONGAn) are some of the most popular indexes used to define glycemic variability. MAGE is the mean glycemia which is the arithmetic average of all the blood glucose readings. The SDT represents the SD calculated for the overall CGM period, so it represents the variability of the whole dataset. The SD is one of the simplest and most effective parameters for assessing glycemic variability, and it has proved closely correlated with most of the other glucose variability parameters. The CONGAn is a recently developed parameter that enables glucose variability to be assessed within defined time windows (the duration of which is indicated by the n value). The IQR is calculated as the difference between the 75th and 25th percentiles of the glucose levels.[71]

In the nonpregnant population, glucose variability was found to be associated with increased oxidative stress[72] and increased rate of morbidity and mortality.[73–77] Egi et al.,[73] in a large study evaluating intensive care unit (ICU) patients from 4 hospitals, showed that the SD of glucose concentration was a significant independent predictor of ICU and hospital mortality. Glucose variability was also found[78] to be an independent risk factor for retinopathy in 130 type 2 diabetes patients with no initial retinopathy and a mean follow up of 5.2 years.

More than three decades ago, Artal et al.[79] studied maternal glucose variability in 154 pregnant diabetic patients hospitalized during the last month of their pregnancies. They found: (1) there was a significant association between maternal glucose variability and neonatal complications; (2) patients with greater glucose variability had more episodes of hyperglycemia, but not hypoglycemia; (3) there was no correlation between maternal glucose variability and the birth weight of the infant. Recent data suggest that glucose variability correlates with pancreatic function and fetal growth.[80,81] In a study[81] of 70 patients (30 with GDM, 20 pregnant women without GDM and 20 nonpregnant women without diabetes) glycemic variability in GDM was higher than in normal pregnant women, and glycemic variability evaluated by MAGE correlates well with impaired early-phase insulin secretion in GDM. However, data regarding the preferred parameter for evaluating glucose variability and its correlation to clinical adverse outcome are limited.

In order to respond to the subheading query above, several conditions need to be met. A sample size should be large enough to provide data on pregnancy outcome; the study should include at least two groups, one using MSMBG and the second CGM and glucose testing must be performed throughout pregnancy since a three-day testing cannot predict level of glycemia. These are the limitations of the current research using CMG. However, we need to be mindful that CGM is still an experimental measure and not a routine clinical tool. The frequency needed for CGM monitoring in diabetic pregnancy and its hypothetical advantage over MSMBG in enhancing pregnancy outcome still needs to be demonstrated.

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12

Innovations in the Application of Advanced Glucose Sensing Technologies to Clinical Decision Making

CGM in Practice

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Science is a very human form of knowledge. We are always at the brink of the known. We always feel forward for what is to be hoped.

—Jacob Bronowski

Key Points

- Diurnal glucose patterns during pregnancies uncomplicated by dysglycemia are characterized by 20% lower glucose exposure and variability.
- Current screening and diagnostic tests for dysglycemia in pregnancy cannot detect perturbations in glycemic control caused by the daily routine of activity and nutrition.
- Maintenance of tight glycemic control in pregnancy is achievable if the underlying dysglycemia can be detected and the appropriate therapy is immediately initiated.
- Continuous glucose surveillance, employing continuous glucose monitoring throughout pregnancy, should be a fundamental tool in the management of pregnancy if mimicking normal glycemia is to be achieved.

The significance of glucose monitoring in pregnancy complicated by diabetes cannot be overstated. Although the evidence remains equivocal as to the precise contribution glucose control provides to the maternal and fetal outcomes of pregnancy, there is no doubt that its importance remains paramount. Perhaps the most potent argument can be summed up by this observation: "if the human body spends so much energy to maintain the blood glucose level within such a narrow range, it is because otherwise it would be deleterious."[1] Pregnancies characterized by normal glucose metabolism have the lowest risk of maternal and fetal complications when compared to those complicated by any degree of dysglycemia.[2–6]

Our studies have shown that women with normal glucose tolerance (NGT) in pregnancy (as measured by oral glucose tolerance test [OGTT] and corroborated by diurnal glucose profiles) are characterized by blood glucose levels (60–120 mg/dL or 3.3–6.7 mmol/L) 20% below those of nonpregnant women without diabetes; and, that this disparity is maintained throughout pregnancy despite an increase in human placental lactogen, consequential insulin resistance, increased maternal weight, and significant changes in diet and activity.[7] These metabolic changes, culminating at the end of pregnancy, are essential for normal fetal nourishment, growth and development, and adequate maternal metabolism. Furthermore, any period of hyperglycemia may be consequential, leading to accelerated and exaggerated fetal growth resulting in large-for-gestational-age or macrosomic infants.[6] Excessively low glucose may retard growth. Oscillating glucose levels, alternating between hyperglycemia and hypoglycemia, may have both fetal and maternal consequences as they have been shown to increase the risk of apoptosis. Therefore, maintenance of glycemic control within a very narrow range in both normal and metabolically challenged pregnancies contributes significantly to the reduction of adverse perinatal outcomes. Consequently, it has become increasingly important to measure and manage the volatility or variability in glucose excursions. With the advent of continuous glucose monitoring (CGM), it has become feasible to

measure and potentially manage the diurnal glucose patterns of women during pregnancy without confining them to bed rest. It is possible to characterize diurnal glucose perturbations and to detect the slightest abnormalities in glucose metabolism under conditions of daily living and potentially ameliorate them.

Until the advent of home glucose reflectance meters, routine prenatal care for the woman with diabetes included blood drawn while in the doctor's office and sent to a laboratory for analysis. For home management, women were supplied with urine glucose testing kits. With the advent of reflectance meters, modern obstetrical practice could instantly measure blood glucose, as could patients at home. But, what did these measures mean? Was a single glucose of 55 mg/dL too low and suggest hypoglycemia or glucose of 180 mg/dL too high and signal hyperglycemia? *Does a single glucose measure have any significance?* To determine this, it is important to note where the glucose came from and where is it going. Shown in Figure 12-1 is a graphic display or modal day of a single glucose value (left side) obtained at 7 AM. Shown on the right two panels are two possible directions from where this glucose came and to where it is going. The difference between the two is significant as in one case (top) the origin is from a state of hypoglycemia and moving toward hyperglycemia, whereas the bottom panel shows the reverse. The clinical decision would be incorrect and potentially a serious mistake if the wrong path were assumed. Suppose, instead, both the origin and the path are known. In this illustration (which represents 288 CGM values displayed according to time), it is clear that if the bottom right panel is followed, the patient is experiencing overnight hyperglycemia proceeded by a lowering of blood glucose after awakening. This is followed by stabilization of glucose within the target range (defined by the two solid parallel lines set at 60–120 mg/dL) until the evening postprandial period when glucose levels rise again. This level of specificity is only possible through use of CGM, which allows for a closer examination of overall glucose exposure.

CHARACTERIZING GLUCOSE CONTROL

In the lexicon of glucose monitoring and diurnal glucose patterns, glucose exposure has become an important concept. Essentially, the clinical question is whether there is excess exposure, where it occurs and at what frequency. Exposure is by convention measured as the area under the curve (AUC). Because a daily CGM tracing produces a single continuous curve, then the area under this curve would constitute exposure and the difference between the patient's curve and the reference or curve for NGT in pregnancy would define or characterize "excess" of "reduced" exposure. To measure glucose exposure, the curve is segmented into 24 equal parts each representing one hour (x axis) and the height of the curve (hourly median) as the y axis. Therefore, AUC = $\sum_{i=0}^{23} P_{50_i}$, where i = hour of the day and P_{50i} = the smoothed 50th percentile value for the ith hour of the day. Note, this value is displayed as mg/dL × 24 hours. For example, in Figure 12-1, the 7 to 8 AM period is 1 × 80 mg/dL= 80 mg/dL/hr and the 9 to 10 PM period is 1 × 110 mg/dL = 110 mg/dL × h. By summing the hourly area for the full day, the AUC is 2100 mg/dL × 24 hours.

As shown in Figure 12-1, the diurnal pattern represents a single day. Is this sufficient data on which to base a clinical decision? The question can be reframed as to whether there are sufficient data to predict the next several days assuming there are no significant alterations in meals and treatment. Figure 12-2 shows graphics that represent three individuals days (1, 2, and 3) of glucose values as well as the three days combined into one modal or representative diurnal glucose profile. Note that each successive day's glucose pattern differs from the one before in several important ways. The overall glucose exposure for each

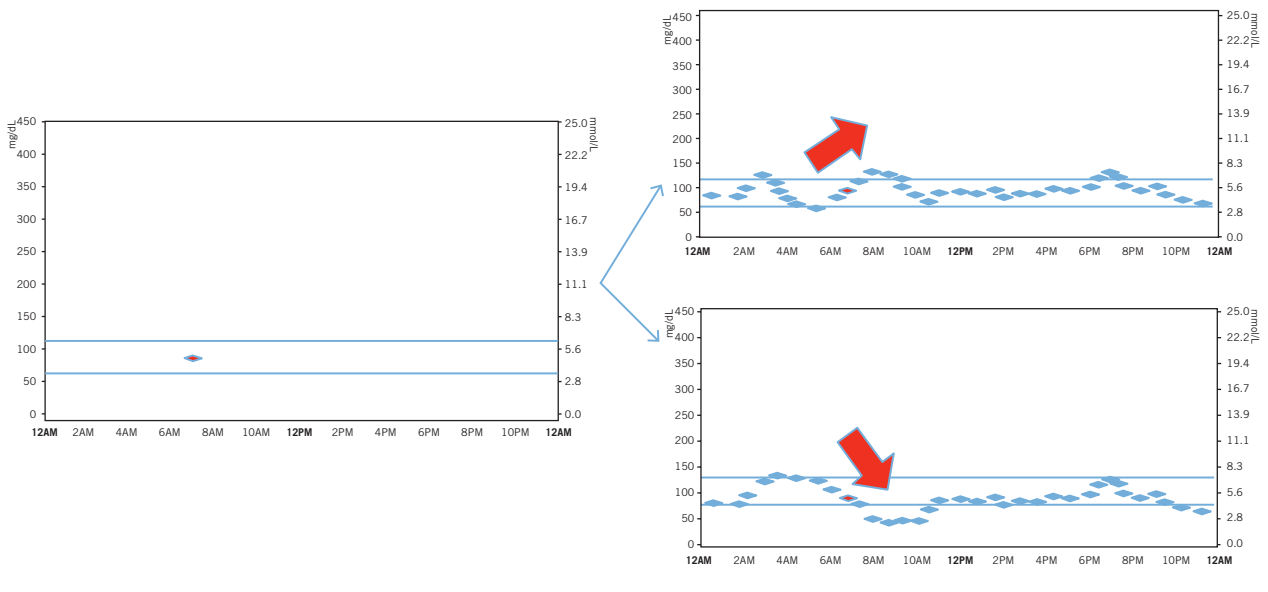

Figure 12-1 Model day with a single glucose value shown with two alternative directions.

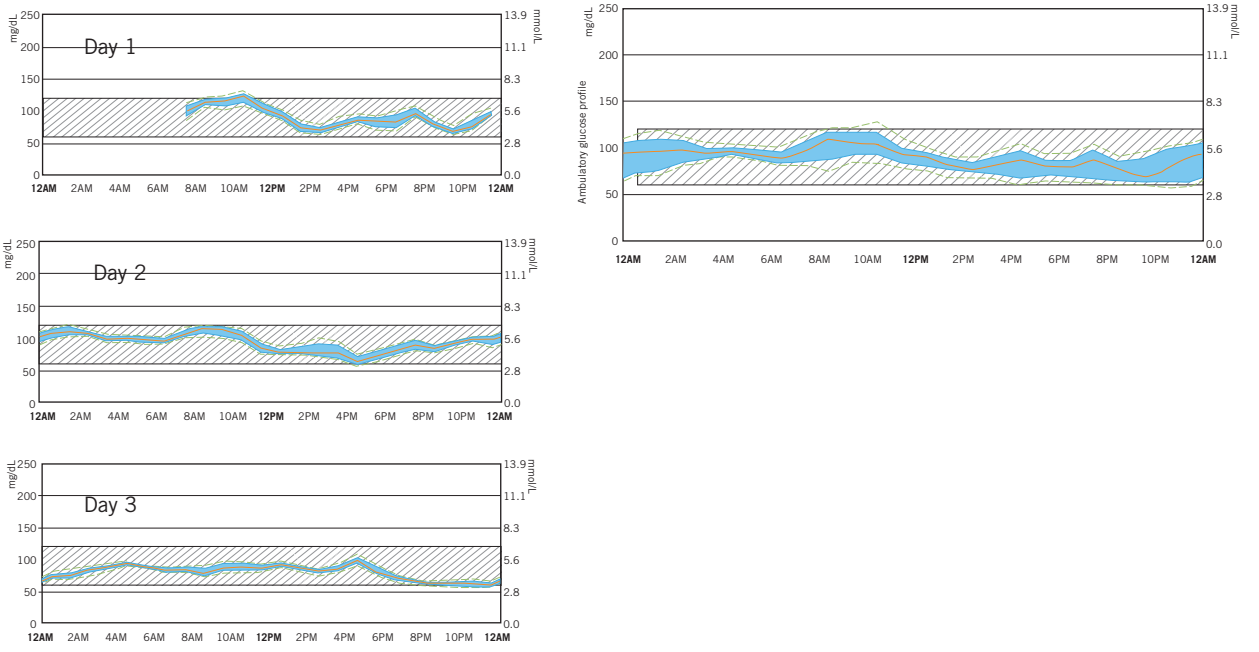

Figure 12-2 AGPs of a single patient representing three consecutive days shown individually and collapsed into one modal day (plotted without regard to date).

day is different as is the variability. To represent these differences, we developed the ambulatory glucose profile (AGP).[8]

As shown in Figure 12-2, right panel, the AGP employs the same individual glucose values that comprise the data from the three individual days; however, it disregards the dates and only considers the time associated with each value. The AGP is depicted by five frequency curves drawn to denote the underlying pattern these glucose values represent. The center curve is the median. At each five-minute time interval, the values are plotted and since more than one day is represented, the median is calculated as the middle value; 50% of all CGM values fall above and 50% fall below this point. In many cases, the mean and median are the same. However, because glucose values are not normally distributed, the mean is replaced by the median in the AGP. The area under the median represents the glucose exposure for multiple days.

The next two curves on either side of the median represent the 25th (lower) and 75th (upper) percentile curves. The area between them (shaded) is called the interquartile range (IQR). For each time period, 50% of all values will be found within the IQR. For example, at 8 AM, 50% of all glucose values fall between 70 and 120 mg/dL, whereas at 4 PM 50% of the values fall between 70 and 90mg/dL. The outlier values (10th and 90th percentiles) are represented by the bottom and top curves (depicted in dotted lines). Ten percent of all values fall below the 10th percentile and above the 90th percentile curves. Examining the AGP, between 10 and 11 PM, 10% of CGM values are below the lower 60 mg/dL and 10% are above 110 mg/dL.

By representing the glucose values as five curves, or AGP, it is possible to rapidly determine whether there is an underlying pattern. In Figure 12-2, the AGP in the right panel shows that glucose levels overnight are variable with 50% (IQR) ranging from 70 to 110 mg/dL, which narrows at 4 AM. Between 7 and 11 AM, the glucose levels remain at the upper limits of the target range they then descend and remain in range until 8 AM. At this point, about 10% of all values fall to hypoglycemic levels from which they do not recover. Two questions emerge: (1) how predictable is this pattern; and (2) is the current intervention efficacious? Xing et al. after a multicenter trial (n = 185) with CGM concluded that 12 to 15 days of CGM are needed to "optimally assess overall glucose control."[9] However, this study was carried out in nonpregnant subjects. Since, in current obstetrical practice, there is a need to rapidly confirm a diagnosis of glucose intolerance, detect the underlying glucose abnormalities, and initiate treatment is the hallmark of successful restoration of euglycemia, we sought to determine the minimum number of days that are sufficient for clinical decision making.[7] We studied 82 women in pregnancy (51 NGT, 25 gestational diabetes mellitus [GDM], and 6 pre-gestational diabetes [pre-GD]). The three-day AGP appeared to be sufficient to establish reference values with consistency. Next the AGPs of the 30 subjects with diabetes were analyzed. The three-day profiles were sufficient to detect underlying metabolic perturbations. In addition, we examined 21 nonpregnant women matched for age (31 ± 7 years of age) with NGT.[8] All women with abnormal glucose tolerance were treated to 80% of values between 60 and 120mg/dL (3.3–6.7 mmol/L). We then determined the mean values for glucose exposure, variability, and percent hypoglycemia. The results are reported in Table 12-1, and reference AGPs are illustrated in Figures 12-3 to 12-5. They are comparable to the findings of other investigators using both longitudinal and in-hospital data for normal pregnancies.[10,11]

TABLE 12-1 Maternal Reference Values for Diurnal Glucose Pattern Characteristics Normalized by Subgroup[7]

Group (Count)	Exposure AUC (mg/dL/24 h)	Variability IQR (mg/dL)	%Hypoglycemia BG <60 mg/dL
Nonpregnant (NGT 21)	2444 ± 165	21.6 ± 4	1 ± 1
Normal pregnant (NGTP 51)	2042 ± 295	23 ± 9	13 ± 15
Gestational diabetes (GDM 24)			
Treated medically (18)	2284 ± 261	35 ± 12	12 ± 11
Diet treatment (7)	2125 ± 110	27 ± 7	10 ± 5
Pregestational (pre-GD 6)	2580 ± 526	50 ± 19	11 ± 7

Abbreviations: AUC, area under the curve; BG, blood glucose; GDM, gestational diabetes mellitus; IQR, interquartile range; NGT, normal glucose tolerance NGTP normal glucose tolerance in pregnancy.

CGM AS A DIAGNOSTIC TOOL

The diagnosis of diabetes in pregnancy has taken on considerable importance with the proposal for altering the diagnostic criteria. What role can CGM play in this debate? Can CGM identify women with underlying abnormalities that go undetected by current screening and diagnostic criteria? Is the OGTT the best diagnostic tool? To address these questions, we re-examined 51 cases of NGT for whom we collected CGM data along with perinatal outcomes.[7] For each case, we produced the AGP from CGM data, measured the newborn weight, and sought to determine whether the diurnal glucose pattern provided early evidence of fetal outcome.

Figure 12-3 shows the AGP report for a woman (23 years old, body mass index [BMI] 38 kg/m^2) whose screening glucose challenge test (GCT) was positive and whose 100 g three-hour oral glucose tolerance test (OGTT) was negative (80, i eat 148, 113, and 97 mg/dL). Following the glucose tolerance test, she underwent CGM. Although at risk for GDM due to her obesity as a result of the OGTT, no further intervention was initiated. As indicated in the AGP, her mean glucose was 90 mg/dL, and her overall glucose exposure was within target. As indicative of our reference cases, 1.5% of her values were within the hypoglycemic range for pregnancy. She delivered at 40 weeks, and the birth weight was 3540 g.

Figures 12-4 and 12-5 show additional cases with NGT based on either GCT or OGTT. In both cases, the birth weights may have been indicative of an underlying dysglycemia not revealed during the standard screening and diagnostic tests. Was there evidence in their AGPs that might have indicated an increased risk of adverse fetal outcome despite the results of the glucose tolerance test?

Figure 12-4 is the AGP of a female aged 23 years with BMI 37.2 kg/m^2. She began CGM immediately following her CGT (1 h 93 mg/dL) in her 24th gestational week. Birth weight was 4270 g at an estimated 41 weeks gestational age (considered large for gestational age [LGA]). Close examination of her CGM data revealed that 19.3% of her glucose values exceeded the top limit of the target range. She averaged 4.6 hours in the hyperglycemic range each day. During periods of persistent hyperglycemia, it is likely that the excess glucose exposure was shunted to the developing fetus. Further evidence indicates that her overall glucose control was mean 101 mg/dL and exposure was 2424 mg/dL * 24 h or 20% greater than "ideal" glycemic control in pregnancy.

Figure 12-5 shows the AGP of a female, 23 years of age, with a BMI of 30 kg/m^2. Because she had no family or personal history of diabetes and no apparent risk factors, she did not undergo screening. She delivered at 37 weeks with fetal weight 2410 g, considered small for gestational age (SGA). Examination of her AGP revealed that her average glucose was 73 mg/dL with 8.4% of CGM below target, spending 4.9 hours each day in the hypoglycemic range. The hypoglycemia appeared chronic as it occurred overnight and well into the day, ending at approximately 4 PM. Although there was no ketone data, the low birth weight may be indicative of fetal undernourishment.

The use of CGM with corresponding AGP analysis as a diagnostic tool remains controversial. These three examples are suggestive of a possible application of this technology in an area of diabetes that has remained mysterious to many. What is the purpose of screening and diagnosis in terms of the discovery of GDM? It would appear that the short-term answer is clear, "to reduce the risk of adverse perinatal, neonatal and material outcomes." Linking the diagnosis to the detection of dysglycemia and furthermore to the identification of the factors contributing to the dysglycemia seems significant. Diurnal glucose patterns provide a unique vantage point for understanding how activities of daily living contribute to glycemic control, which was not feasible prior to the advent of CGM. Should everyone undergo a period of CGM during pregnancy in place of or in addition to more standardized testing, perhaps. Current technology makes this unfeasible but raises the question as to who should be considered for this level of investigation. The examples of three women who were deemed to have "NGT" revealed that the woman with the high-risk profile due to obesity (Figure 12-4) produced a healthy child; the woman with a similar profile produced a macrosomic infant and the woman with no risk factors produced a small for gestational age (SGA) infant. It would suggest that in the three cases since the AGPs were distinctive, they may have been useful.

CGM AS A THERAPEUTIC TOOL

It had been assumed axiomatic that with the additional information available through self-monitored blood glucose (SMBG), perinatal outcomes would improve. The evidence is somewhat equivocal although leaning in favor of a beneficial effect when

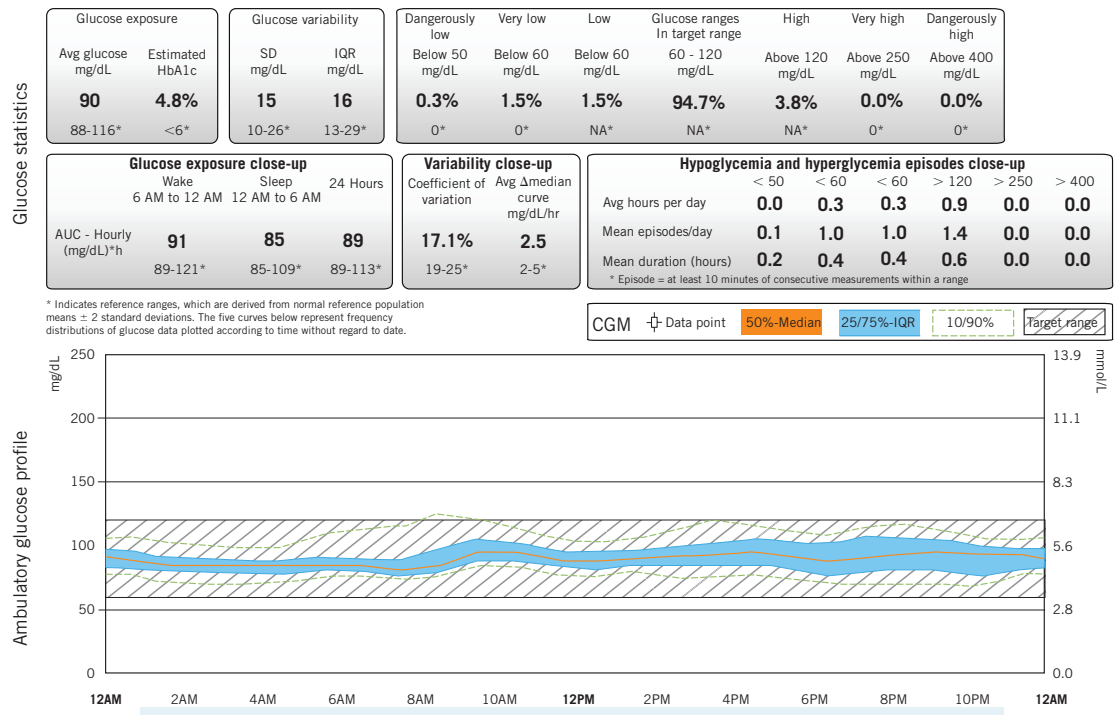

Figure 12-3 AGP of subject with normal OGTT.

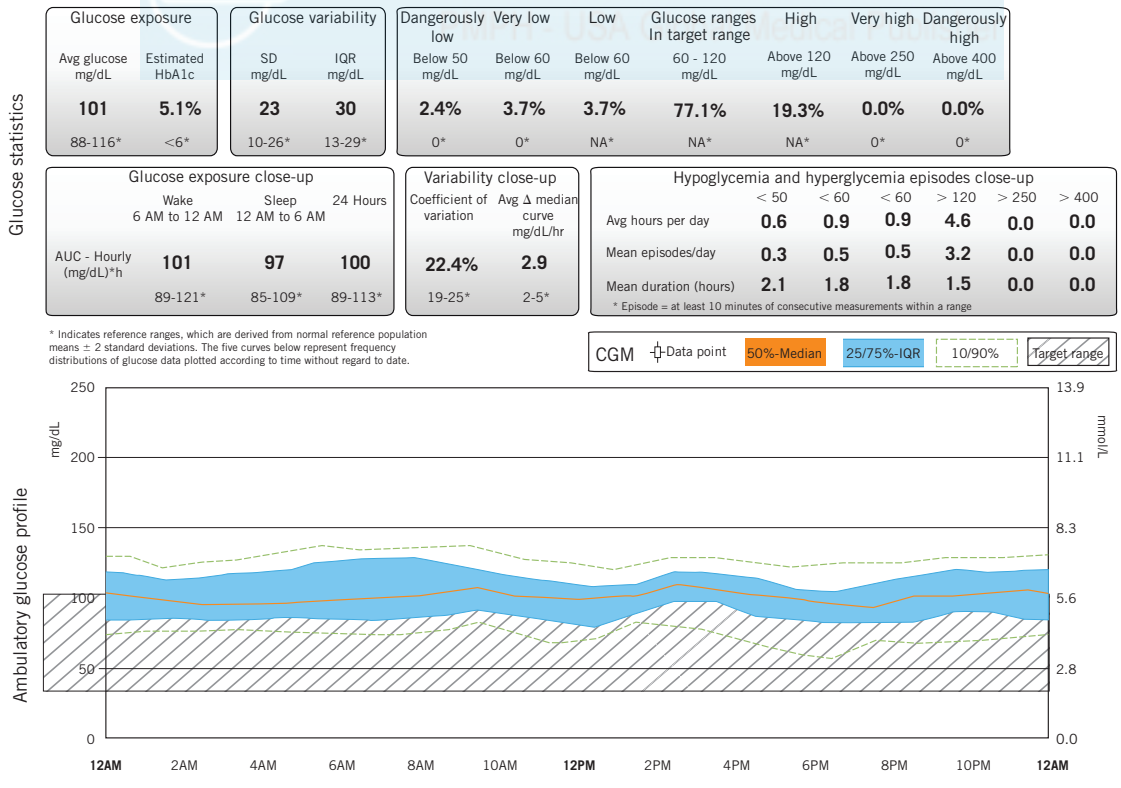

Figure 12-4 AGP for subject with normal glucose tolerance based on screening GCT.

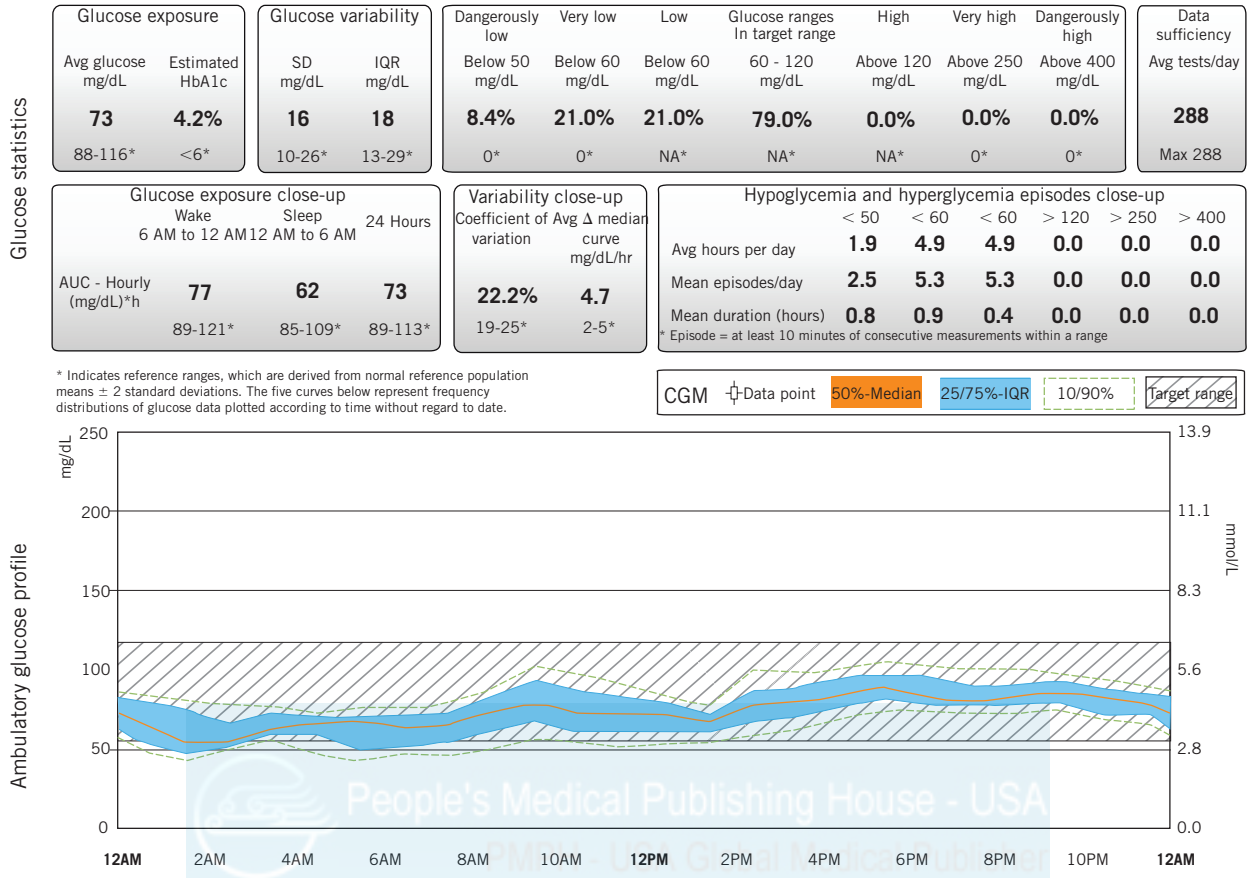

Figure 12-5 AGP of a subject considered free of risk factors and consequently believed to have normal glucose tolerance.

used properly. With the advent of CGM, the axiom should take on even more significance. Twenty-four-hour uninterrupted monitoring should provide a physiologic framework for clinical decision making in three general areas: (1) detection of the underlying dysglycemia; (2) selection of the most efficacious therapy; (3) measuring treatment effectiveness and guiding adjustments. Can CGM assist in detecting even the slightest dysglycemia in a manner that will guide treatment decisions? In our analysis of patients treated with diet only therapy and periodically monitored by CGM over a period of seven months, we could identify underlying dysglycemia heretofore impossible to detect.[7]

Figures 12-6 and 12-7 track the progress of a 37-year-old woman (parity 0) with a BMI of 19.2 kg/m^2 who underwent an OGTT in her third month of pregnancy. The results (fasting: 81 mg/dL, 1 hour: 108 mg/dL, 2 hours: 187 mg/dL, 3 hours: 101 mg/dL) indicated GDM due to the combination of one abnormal value (3 hours) and the timing of the OGTT. Rather than repeating the OGTT in the third trimester, the clinicians decided to place the patient on a restricted diet comparable to that used for patients with GDM (40% carbohydrate, 20% protein, and 40% fat) and periodically monitor her on a monthly basis employing CGM followed up by alterations in treatment if required. Figure 12-6 depicts the AGP for the period immediately following the OGTT and the next month. In the left panel, the initial AGP showed that the mean glucose was 77 mg/dL with an IQR (variability) of 27 mg/dL. Overall glucose exposure was 1872 mg/dL × 24 hours. Did the profile corroborate the clinical decision to initiate dietary treatment? Closer examination revealed significant and prolonged overnight hypoglycemia with 21% of the CGM values below 50 mg/dL. The uninterrupted hypoglycemic episodes lasted on average 1.3 hours; and there were four such episodes each night. The AGP clearly indicates that the episodes begin at midnight and continue periodically until 8 AM. Had only SMBG been available, it would have produced a consistent within target fasting as the patient awakened after 8 AM. Once awake, the patient's diurnal glucose pattern changed. Generally glucose levels remained within the target range with periodic excursions (10 AM to 12 noon, 3–4 PM, 7–9 PM, and 10–11 PM) into the hyperglycemic range (shown in dashed lines). Constituting 7.4% of the CGM values, these hyperglycemic excursions lasted on average 40 minutes. The combination of significant hypoglycemia with periodic hyperglycemia appeared to corroborate the original diagnosis. Since the initial discovery occurred early in pregnancy, dietary intervention with close monitoring could be initiated with low risk of worsening the dysglycemia.

The first task appeared to be a reduction in the risk of severe hypoglycemia. As shown in the right panel of Figure 12-6, the change in treatment (increase in carbohydrate proportion)

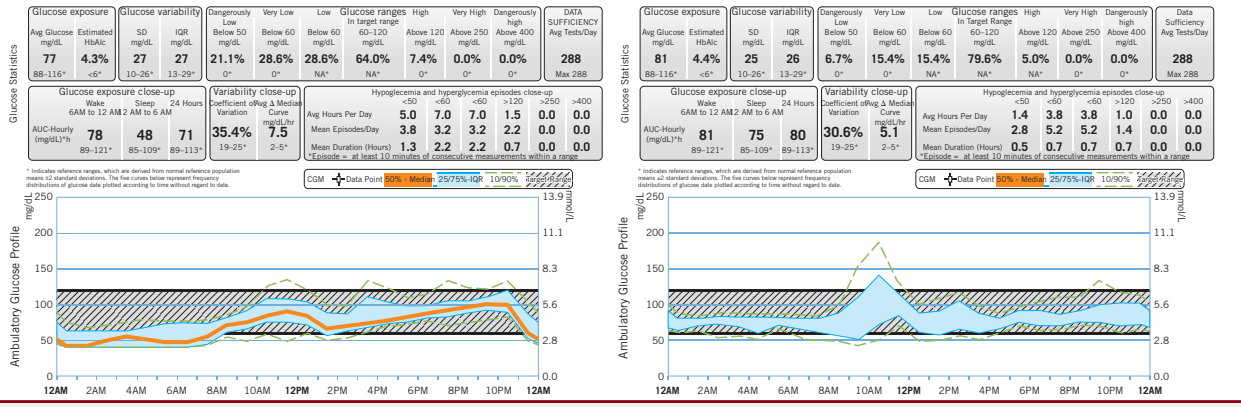

Figure 12-6 AGPs representing the 12th (left panel) and 16th (right panel) gestational weeks of pregnancy.

significantly reduced the incidence of severe hypoglycemia to 6.7% and the duration to 30 minutes. It also moved the hypoglycemic episodes to daytime (8 AM to 4 PM). As illustrated in the AGP, there was a significant increase in the breakfast postprandial glucose excursions reaching as high as 200 mg/dL. However, since this was limited to one time period and dietary related, the intervention could be focused. Further examination revealed that the proportion of values within target had risen to 79.6% and that the mean glucose (8 mg/dL) and glucose exposure (1944 mg/dL × 24 hours) were within target.

The second sequence of AGPs (Figure 12-7) was completed during the 8th and 9th months of pregnancy treated with diet only therapy. As shown in the left panel, the attempt to ameliorate the postprandial hyperglycemia failed. Peak glucose levels at mid-day increased to 200 mg/dL. Overall, mean glucose level increased to 95 mg/dL with 68.2% within target and 19.8% above target. Excess glucose exposure was 400 mg/dL × 24 hours, which is 20% above target. On a daily basis, the patient averaged two episodes of severe hypoglycemia, each lasting 90 minutes. The first episode occurred overnight. Due to the wide variability, the episode would be unpredictable. During some days, the glucose would be in target, while on other days, the glucose would be below target. The second episode occurred between 5 and 7 PM with less certainty than the overnight hypoglycemia. The wide IQR is indicative of inconsistent patterns related to nutrition and activity making it difficult to adjust treatment. Nevertheless, by the next monitoring period, one week prior to delivery (shown in the right panel), the postprandial hyperglycemia was resolved, much of the overnight hypoglycemia was corrected and the overall variability was reduced. This resulted in a lower mean glucose and consequently near normal glucose exposure. This raised the proportion of values within target to 82.7%. Birth via vaginal delivery occurred at 38.2 gestational weeks and birth weight was 3230 g.

The review of this sequence of AGPs representing six months of pregnancy revealed findings that heretofore were generally hidden, especially in GDM treated by diet only. Most prominent was the identification of repeated episodes of (<60 mg/dL) hypoglycemia. Examination of all women treated by diet only therapy in this series revealed that they ranged from 10% to 20% hypoglycemia. When compared to women treated with pharmacologic agents, the range was almost identical 12% versus 10%, respectively. In this case, postprandial glucose excursions were >200 mg/dL suggesting the possibility of underlying type 2 diabetes, which would not have been supported by her BMI and therefore unlikely to be under surveillance. Comparing all women with diet only treatment with women treated with pharmacologic agents, less than 0.5% of the time patients diet only treatment experience resulted in glucose >200 mg/dL, whereas patients treated with pharmacologic agents had nearly triple the incidence. Further analysis of CGM data showed that women treated with pharmacologic agents had greater variability (IQR 27.4 vs. 34.4 mg/dL) and glucose exposure (2125 vs. 2284 mg/dL × 24 hours) than women treated with diet only.

Close examination of the relationship between the CGM data and maternal/fetal biophysical parameters revealed that women treated with pharmacologic agents tended to be heavier (BMI 33 vs. 22 kg/m^2) and their offspring larger (birth weight 3188 vs. 2973 g). This would be predictable based on their greater glucose exposure. In this series of women, the OGTT was consistently higher for the insulin- or glargine-treated group when compared to diet. This is not surprising as the initial clinical decision was made based on the results of the glucose tolerance test.

What then did CGM with AGP analyses contribute? Before examining the question, the same study series collected AGPs on patients with pregestational diabetes. Figure 12-8 shows the AGP of a 26-year-old woman with BMI 26.6 kg/m^2 with type 1 diabetes in her third trimester treated with basal/bolus insulin. In comparison to the subject shown previously, this subject exceeds the other in all AGP characteristics except hypoglycemia. Glucose exposure is more than 20% above target and glucose variability is twofold greater than the target. Less than half the CGM values are within target. Consequently, the patient spends 15% of the time in hypoglycemia and 40% in hyperglycemia. The wide variability throughout the day and overnight makes clinical decision making especially difficult. Virtually at every time period, there is a risk of hypoglycemia if too much insulin is administered to overcome the hyperglycemia. The two highest risk periods are 4 to 6 AM and 5 to 7 PM. At these times, there is an equal risk of hypoglycemia or hyperglycemia. This is due to the day-to-day differences in glycemic control. The period of least risk of hypoglycemia

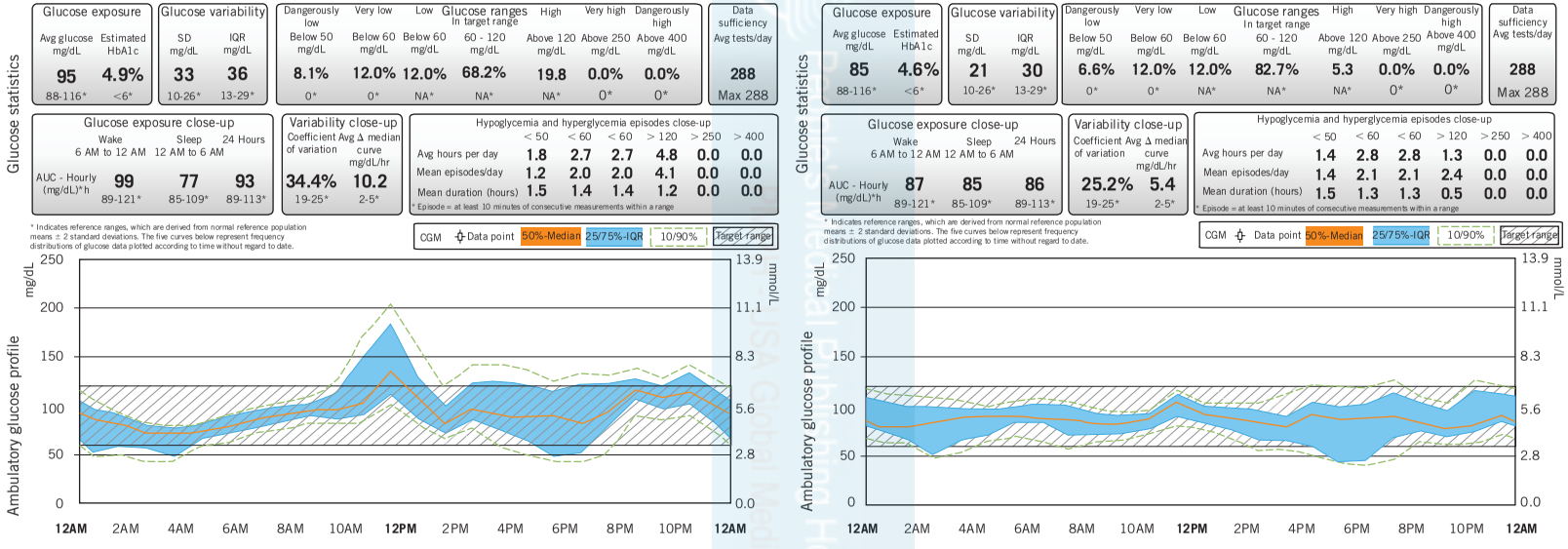

Figure 12-7 AGPs representing the 32nd (left panel) and 37th (right panel) gestational weeks of pregnancy.

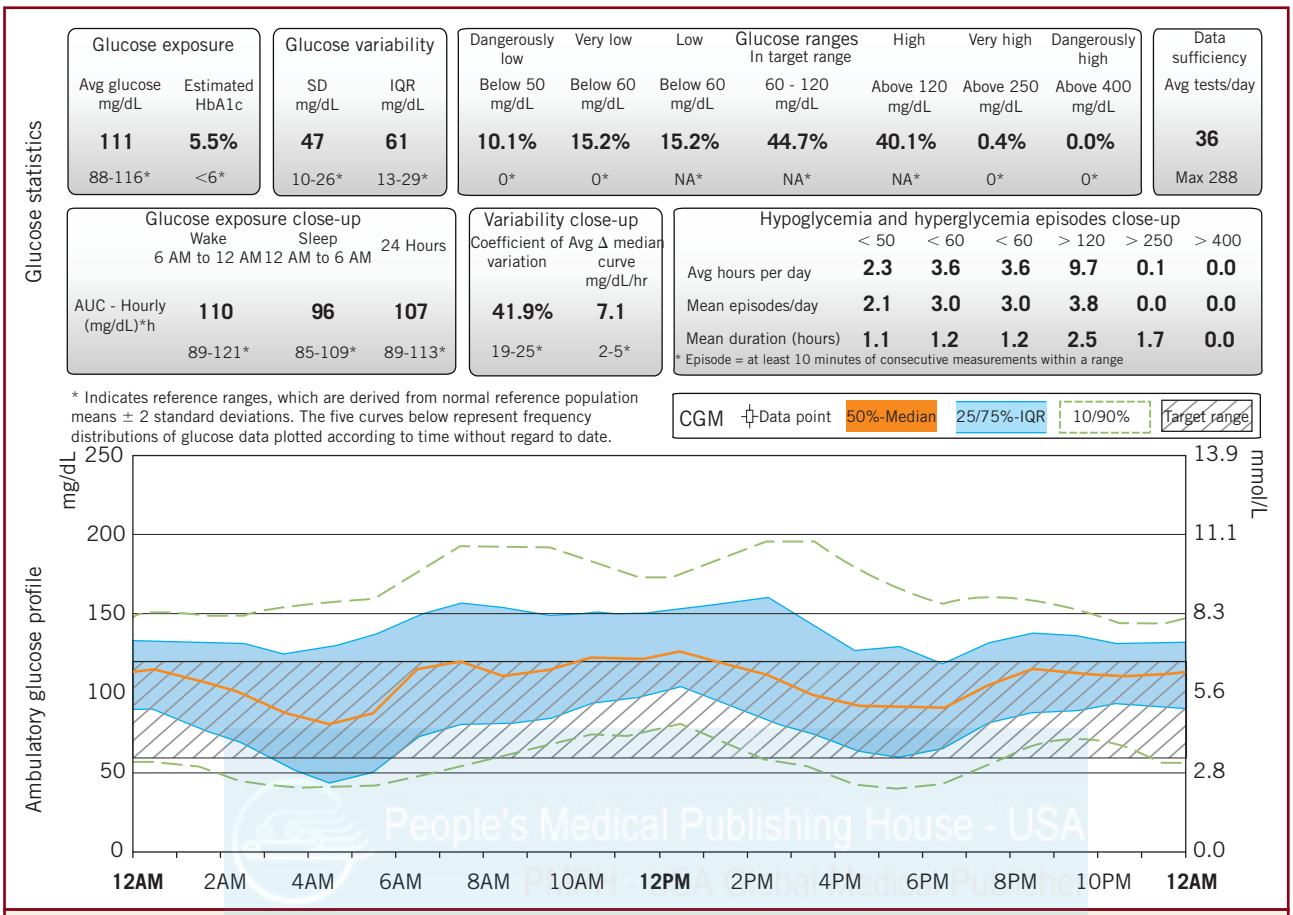

Figure 12-8 AGP of subject with type 1 diabetes in pregnancy.

and consequently the greatest likelihood of succeeding in overall reduction in glycemia is 8 AM to 2 PM. Not surprisingly this period extends from breakfast through lunch. Dietary changes are likely to reduce the high glucose during this period and to lessen the variability. This step takes precedence. The next step would be to reduce the basal insulin to correct the hypoglycemia, but only after the dietary changes are evaluated.

The importance of tight glycemic control in minimizing perinatal complications is well documented. In the absence of CGM, the task is limited by the willingness on the part of the patient to monitor as much as seven times each day and in the cases just reviewed overnight as well. Realistically, this is a daunting task often with inadequate results. In light of the evidence that normal pregnancies are portrayed by tight glycemic control, which has been characterized as 20% lower than that of a normal nonpregnant individual with diurnal glucose levels remaining within a narrow corridor (between 10 mg/dL above and below the median), it is incumbent to find a means to reach this goal. Failing to achieve tight glycemic control increases the risk of LGA and macrosomia, cesarean delivery, shoulder dystocia, fetal malformations, neonatal hypoglycemia, jaundice, and stillbirth.[12,13] For women with preexisting diabetes, the American Diabetes Association (ADA) advises achievement of HbA_{1c} levels below 6% prior to pregnancy to attain perinatal risk levels comparable to normal pregnancies.[14,15] This may suggest that for such individuals, CGM should start prior to conception. In addition to optimal HbA_{1c} levels, the ADA suggests that pre- and postprandial glucose levels in all pregnancies complicated by diabetes should mimic those found in normal pregnancies. However, in pregnancy, the use of HbA_{1c} is limited.[16] The need to have immediate feedback as to the efficacy of treatment and to rapidly identify periods of high risk all but rule out its use. HbA_{1c} does not reflect and cannot detect hypoglycemia. Although it can suggest hyperglycemia and glucose variability, it cannot pinpoint their frequency, duration or contribution to overall glycemic perturbations. While determining an individual's HbA_{1c} level may be an applicable method of estimating gross glucose levels (e.g., mean glucose level of past three months), it does not present a measure of daily glucose variability.

The cases reviewed confirmed that diurnal glucose patterns during pregnancies uncomplicated by dysglycemia are characterized by 20% lower glucose exposure and variability. Second, maintenance of this narrow range in pregnancy is achievable if the underlying dysglycemia can be detected. Third, continuous glucose surveillance, employing CGM throughout pregnancy, should be a fundamental tool in the management of pregnancy if mimicking normal glycemia is to be achieved.

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Patient Compliance

The Elusive Variable in Diabetes Management

13

Nieli Langer, PhD

Be kind, for everyone you meet is fighting a harder battle.

—Plato

Key Points

- Women with diabetes in pregnancy need person-centered customized medical and behavioral goals to enhance treatment compliance.
- Person-centered diabetes care may improve patient satisfaction.
- Culturally competent patient/physician communication may enhance adherence and clinical outcomes.

INTRODUCTION

The struggle to cope with diabetes in pregnancy is continuous since diabetes management requires constant vigilance. No single helping strategy meets all the varied needs and situations that confront persons with diabetes. Many of the problems and crises of diabetes management in pregnancy have emotional and psychosocial sources rather than medical ones. Pregnant diabetic women often feel anxious and even depressed when faced with trying to balance a diabetic regimen, the pregnancy state, and the need to maximize quality of life. Many studies have shown a correlation between glucose control and psychological factors such as mood disturbances.[1–3] We[1] found that the use of self-monitoring blood glucose (SMBG) with multiple determinations appears to positively affect the emotional state of the patient who maintains the established levels of glycemic control.

Pre-existing diabetes is a chronic disorder in which the woman is exposed to the seemingly random metabolic glucose fluctuations and is constantly faced with an ongoing struggle to control the illness without letting it control her life. We[2] reported that chronically ill pregnant diabetic women display significantly greater anxiety and hostility in comparison to non-diabetic women. However, regardless of the level of glycemic control achieved or the severity of the disease, mood states were *not* affected in these diabetic subjects. Many chronically ill patients are often unable and/or unwilling to achieve established medical goals due to physical, social, cultural or psychological limitations; they have become resigned to their situation.

Near normal glycemic control is associated with decreased complications for both gestational diabetes mellitus (GDM) and pregestational women. The established levels of glycemic control in pregnancy may be achieved with a strict management approach using either insulin or glyburide therapy. The quality of glucose control often affects psychological adjustment while psychological adjustment affects glycemic control.[4] Patients work hard to achieve the established levels of glycemic control only to experience a sudden loss of control with a hypoglycemic episode. Therefore, the care of the pregnant diabetic patient involves both medical and psychological care, that is, "whole-person care." When providing this type of care, it is necessary for the physician to have an understanding of the "lens" through which patients view their lives and the disease that inhabits their lives. Physicians are able to provide enhanced whole-person care when they focus on patients' capabilities, assets, and positive attributes rather than problems and pathologies. However, sometimes provider care focuses on the "d-words"…decline, disease, disability rather than on the "h-words"… hope, help, harmony. When physicians focus only on patient deficits, interventions often remediate, minimize, or compensate; when the attention centers on patient strengths and assets, interventions maximize and expand upon these strengths. We as health professionals must look past the superficial characteristics of our patients and aim high. To set low standards and low expectations is a disservice to everyone we counsel. In other words, assume that each of your clients is intelligent, motivated, and eager to apply exactly what you teach. Then, no one will be underserved.

While long thought of as a "soft science," communication is increasingly understood to be at the root of many health cares' failures. Care providers need to be reminded that patients are often afraid, confused, and always anxious. They want reassurance that the people providing care really understand what it is like to be a patient. Patients want better communication between themselves and care providers as well as enhanced communication between providers so they feel that someone is taking responsibility for

their care.[5] Miscommunication has resulted in patients often not understanding or retaining what doctors say, that is, patients don't always read or understand information in a consent form; they often forget information they have been given as soon as they leave the office; and, what patients recall after leaving the physician's office is often incorrect.[6] Physicians need to recognize that some interactions will not go well, but that they can walk away with the feeling that they did the best they could to maintain their professionalism and compassion despite challenges coming from multiple directions. Once these stresses are acknowledged, health promotion can then focus on maximizing a person's desire for independence by promoting self-reliance rather than dependency or learned helplessness.

Kobasa[7] hypothesized that people with the greatest control over events in their lives will remain healthier than those who feel powerless. However, an understanding of inner strength as it encompasses well-being and self-nurturing practices is necessary for health professionals to facilitate and enhance the health and quality of life for patients. *Strengths perspective communication* between practitioner and patient involves working together to seek and implement the best solution (after considering several alternatives) for patient management of a diabetic protocol.

The strengths perspective model assumes that

- People are responsible for and capable of making their own decisions.
- People are often able to direct their lives more than they realize; they have some freedom to choose even if their options are restricted by environmental variables or inherent biological or personality predispositions.
- People are continually motivated to address their needs from basic physiology to abstract self-actualization.
- People are capable of learning new behaviors and unlearning existing behaviors; they strive for reinforcements that are meaningful and congruent with their personal values and belief systems.[8] The author captured the rationale for the strengths perspective with the following challenge:
- At the very least, the strengths perspective obligates practitioners to understand that, however downtrodden or sick, individuals have survived (and in some cases thrived). They have taken steps, summoned up resources, and coped. We need to know what they have done, how they have done it, what they have learned from doing it, and what resources (inner and outer) were available in their struggle to surmount their troubles. People are always working on their situations, even if just deciding to be resigned to them; as helpers, we must tap into that work, elucidate it, and find and build on its possibilities.

This chapter offers care providers an approach to person-centered diabetes management as a way to improve patient satisfaction and clinical outcomes.

BACKGROUND

Patient nonadherence (noncompliance) with therapeutic regimens is recognized as a challenge to the successful delivery of health care. However, patients and care providers look at compliance through very different lenses. Medical paternalism (physician-directed practice) at one end of the care continuum and patient self-determination at the opposite end need to create a balance in the form of whole person care that will foster patient compliance. Doctors value compliance as a necessary component to treatment. The compliance model, synonymous with concordance or adherence,[9] also promotes the idea that health professionals know best and that patients have an obligation to follow the direction of professionals since the benefits of compliance outweigh the impact (e.g., social, psychological, economic) on the patient's life. For the physician, patients' noncompliance is synonymous with disobedience. Noncompliant or nonadherent patient behaviors include:

- *No-show* to appointment
- *Not* having the prescription filled
- *Not* taking the correct dose or forgetting to take the requisite number of doses
- *Not* taking the medication in a timely manner
- *Discontinuing* the medication without medical consultation

Traditionally, medical training has focused on diagnosis and treatment of a disease with the notion that if these two factors are satisfactorily managed, the desired outcome will inevitably follow. When it does not, physicians often attribute failed outcome to patient noncompliance. Perhaps the first and most important step in creating the foundation for empowerment for patient diabetes management lies in an examination by the physician of his own expectations and an understanding of the role these expectations play in the physician–patient relationship. Unfilled expectations on the part of the physician can lead to labeling the patient as noncompliant and her behavior as inappropriate and unreasonable, when, in reality, the behavior demonstrated may be completely acceptable in the patient's sociocultural location. Labeling a patient as uncooperative or noncompliant due to the physician's unfulfilled expectations can destroy the trust and respect necessary for effective interaction. Physician expectation that the patient will accept the medical model is a central problem with the way they think about compliance because patients are often unwilling or unable to comply with physician instructions.[10]

Patients have a responsibility to participate in their own health care. A patient's failure to do so might be considered contributory negligence in the event of a poor outcome. The reality, however, is that it is the physician who is expected to take the ultimate responsibility and who will be sued in the event of adverse perinatal outcome. A missed or canceled appointment could mean an irresponsible patient. It could, however, also be a sign that there is a breakdown in the communication between the physician and patient. No-show patients should never be ignored. Today, it is recommended that physicians document a no-show. It is also prudent to find out why the patient did not keep the appointment and to document her explanation.

Patients value convenience, money, cultural beliefs, habits, body image, and so on. They are at liberty to reject medical advice, and often do, even though they might not tell the physician. Patients use their judgment when presented with medical advice even though they may not have the professional expertise claimed by physicians. Failure to heed advice from other professionals, that is, lawyers or accountants may have serious consequences but these professionals see this independence as part of clients' rights. They do not see it has client deficiency but rather as an indication, perhaps, that they may need to improve the services they offer.

As the literature on noncompliance indicates, the medical model that expects patient compliance (adherence) is not effective in diabetes care.[9,11,12] Patients are not interested in diabetes; patients are interested in *their* diabetes. The changing cultural environment is increasing its insistence on a more cooperative relationship between doctor and patient, with the patient taking a more active and informed role than ever before.[13] *Empowerment* recognizes that a patient needs to learn the skills, acquire the knowledge, and therefore, achieve the power, to enable her to play a leading role in her own diabetes management. To manage diabetes successfully, patients must be able to set goals and make decisions that are both effective and fit their values and lifestyles while addressing physiological and psychosocial factors. This paradigm recognizes that in the patient-provider relationship, the doctor and patient each bring his/her own expertise to the medical encounter and each respects the ideas of the other. In diabetes, this means the recognition that while health professionals are experts on diabetes care, patients are experts on their own lives. The role of a patient is to be a well-informed active partner in her care. The role of the professional is to help patients achieve goals and overcome barriers through education, appropriate care recommendations, and support.

Knowing about an illness is not the same as knowing about a person's life, and since the disease affects the person's life, patients need to be the primary decision makers. Patients are the best sources of information about the attitudes, beliefs, and lifestyle issues that affect their acceptance of medical treatments. Patients often feel overwhelmed by the huge amount of effort involved in staying well. They often have the experience of doing everything right and still failing. People with diabetes often view life in "black and white" terms, that is, perfection or failure. Therefore, they may sometimes avoid all diabetes issues, tests, and even visits to the doctor. These issues should not be confused with apathy; they are angry and conflicted about their disease. They know that they need to manage their diabetes, but they don't want to. Listening for patients' meanings and values then becomes the starting point for gaining patients' adherence. Although the idea of empowerment seems to be an ideal in helping people with chronic diseases, with a noncompliant patient, care providers often do not know where to start. One physician in desperation asked his unmotivated, noncompliant, and uninterested diabetic patient, "Well, what would you like to do?" Working with the patient to reach agreement on a treatment plan that makes sense in the context of her life will facilitate her adherence to self-management when she leaves the physician's office and resumes her day-to-day life.[12,14,15] Satisfaction, communication, and consultation style are all factors in the doctor–patient relationship. Research on adherence is converging on the doctor–patient interaction with patient satisfaction and communication style critical to patient outcomes. Empowerment, resulting in whole person care, makes good human, clinical, and economic sense.

VARIABLES RELEVANT TO PATIENT MANAGEMENT

There is paucity of consistent evidence to demonstrate that the factors of age, gender, or socioeconomic status are associated with adherence.[16] Likewise, no personality type has been found to be consistently related to nonadherent behavior. However, research in the area of patient perception of social support has indicated a positive association to adherence to a medical regimen. When patients perceive sufficient levels of practical, emotional, and cognitive social support and when relationships within the patient's circle of family and friends are stable, then adherence levels are high. Emotional and moral support from the family may help to reduce the patient's anxiety about medical appointments; cognitive support from family may help the patient understand her medical condition. It may also enhance the rationale for maintaining the diabetic protocol and keeping medical appointments.[17,18]

The *Health Belief Model* is the patient's belief in his/her own susceptibility to a disease or illness. It is the belief regarding the degree of severity of the illness and the consequences for health and daily functioning; belief in the efficacy of the treatment for the illness; belief about the barriers and costs related to treatment; and cues to action. Each of the components has been shown to influence the degree to which a patient will/will not adhere to a treatment regimen.[19] The model has valuable retrospective value in measuring adherence to a regimen but disappointing prospective value.

The type of illness and levels of adherence have also been found to have a minor relationship. Treatment variables that significantly affect adherence include side effects, intrusiveness, complexity, and duration. The weight of evidence suggests that the presence of side effects may decrease adherence; anticipatory fear of side effects can also affect proper adherence to medical regimens.[20] In addition, if the potential diabetic treatment intrusions are high, such as interruption of daily activities, and if emotional and financial costs are high as well, nonadherence will more likely occur.

Researchers have reported that patients either deliberately falsify or accidentally misreport adherence data. Mazze et al.[21] first reported this problem in studies related to ambulatory SMBG in which a memory chip in meters substantiated patient self-reports. Researchers asked patients to record the results of blood glucose results in a logbook. The patients were not told that the glucose meters they were using had a memory capacity. The researchers compared the logbook values with the values stored in each meter's memory. Findings indicated that >70% of the patients overreported glucose readings and that >30% of the entries were fabricated. The results indicated a pattern of fabrication and imprecision that significantly altered the actual clinical profile of the individual with diabetes. When investigators informed the women of the memory capabilities of the meters, recording accuracy dramatically improved.

In diabetes, pregnant patients are expected to follow a complex set of behavioral actions to care for their diabetes on a daily basis. The treatment for diabetes often involves a complex regimen that varies across patients and in different situations. Self-care in diabetes is fluid rather than static, and the regimen resembles more of a series of "if-then" statements rather than a standard medical prescription.[22] Lifestyle behavior may include meal plans and physical activity; adherence to a medical regimen (insulin or oral hypoglycemic agent) when indicated; monitoring blood glucose; and seeking individually appropriate medical care for diabetes and other health-related problems. Regimens vary from patient to patient. In addition, patients with diabetes are often required to make very complex treatment decisions.

They may be required to vary their self-care behavior from situation to situation with often no standard behavioral model to follow. This all-encompassing protocol then needs to be integrated into a patient's daily life.

CULTIVATING SKILLS THAT PROMOTE PATIENT SATISFACTION AND CLINICAL OUTCOMES

Strengths perspective communication fits well with patient empowerment. The strengths perspective focuses on capabilities, assets, and positive attributes rather than problems and pathologies. This generative model enhances patients' resources for problem solving, coping, and healing. It appears to add an element of control, at least internally, which is very important to a sense of well-being. Listening and attending behaviors that communicate empathy, encouragement, support, respect, and nonjudgmental acceptance are the most effective in implementing an environment of empowerment and potential adherence.

Probably the most basic and powerful way to connect to another person is to listen. Perhaps the most important thing we ever give each other is our attention. We connect through listening. Active listening refers to nonverbal communication such as eye contact—look at patients when they speak. It involves verbal behavior such as responding to the patient by reflecting: using comments such as "I see what you mean" signaling that you are listening and encourages the patient to continue. It also involves avoiding sending discouraging messages by interrupting, changing the subject, or not acknowledging what the patient says. Patients are empowered because they feel worthwhile as human beings, feel accepted by the care provider, and are, therefore, comfortable to explore how to achieve adherence. Unhelpful communication behaviors may include interrupting the patient's explanation, preaching, blaming, extensive probing, and questioning, especially with "why" questions and adapting a patronizing attitude. These behaviors are hindrances because they put patients on the defensive and make them feel so worthless that they will naturally choose avoidance rather than approach behaviors that facilitate adherence.[23,24] Empowerment is not just an abstract philosophical concept. A practical attitude and environment is attainable when conditions of genuineness, respect, and empathy are generated and used to facilitate whole person care.

For most patients, physician competence and communication are equally important. Researchers have linked poor communication to misdiagnoses, the ordering of unnecessary tests, and the failure of patients to follow treatment plans. An article in the *New York Times* (June 2004) reported the results of a series of studies that good doctor–patient communication resulted in lower blood sugar levels in diabetic patients and lower blood pressure in hypertensive patients. The message conveyed that if patients believe they are in a good relationship with their doctors, there is a strong chance their health will benefit, too.

"Technology has become a religion within the medical community. As a result, it is easy to lose sight of the fact that still, in the 21st century, it is believed that 80–85% of the diagnosis is in the patient's story."[25] Yet medical educators say that doctors are insufficiently trained to listen to those stories. After all, there is no reimbursement category on insurance forms for listening. Medical ethicist Arthur Frank describes the process of a patient seeking care from a doctor as one of "agreeing to tell her story in medical terms…"[26]

Actively listening to the patient's experiences and using them as the starting point for gaining adherence may be the first step. When a patient's concerns are validated, perceived problems become less of an issue. The lost art of listening has been the inspiration behind a growing movement in medical schools throughout the country to comprehend the health care needs of patients: *storytelling or narrative medicine*. Communicating by storytelling is fundamental to the human experience and is a powerful medium for communicating, learning, and problem solving, whatever the language or culture. The story as a linguistic form has specific characteristics such as: it requires both a narrator and a listener whose different viewpoints are brought to bear on how it is told; it focuses on characters—what they do, and what happens to them; and it includes an emotional dimension, that is, how the characters feel about what is happening. Stories presented in this context are often negative, full of problems, and difficulties.

"*Restorying*" is about developing patient stories in new directions. The new story makes action and change possible. People grow from strength, not from weakness. Positive regard and respect for the patient are essential for growth and adjustment. When the physician develops with the patient a list of strengths and assets gleaned from the dialogue, he will find that he can draw on these assets later for possible resolution of concerns and problems related to the management of the diabetes.

Aspiring doctors need to learn to pay attention to what their patients are saying and to understand the way their own emotions affect their perceptions and ultimately their clinical practice. How often does a patient try to tell a doctor what happened in a sickness and the doctor interrupts with, "What was the pain like, sharp or dull?" The interruption prevents the patient from unfolding the account and inhibits the physician from gleaning diagnostic accuracy from a full picture. Doctors have continually been admonished that they do not understand what their patients' experience. Today, medical schools are attempting to insert the missing communication skills in medical school syllabi that may facilitate more humane patient-care provider interaction.[25]

There is a growing academic literature that gives theoretical basis for the narrative as a more sophisticated tool for recording and analyzing an illness than the conventional clinical interview. Research has shown how the narrative is suited to revealing worlds that are otherwise closed to professional practitioners—such as those burdened with a chronic disease. It is conceivable that the narrative will enable professionals and their agencies to convert stories into action that may help facilitate the provision of a new service. There is paucity of information in the literature on how best to use storytelling as a means for gaining a holistic understanding of patient predicaments and its impact on the individual and his/her community. However, there is reason to take note that although stories are simple human forms of expression and communication, they have the potential to be powerful tools for achieving understanding, building a shared perspective on a medical problem, and catalyzing change.[27]

Although many medical schools have introduced some form of communication training, so have the organizations that run the continuing medical education courses required for renewal of medical licensure. Even health maintenance

organizations, recognizing that doctors who are good communicators improve the bottom line (their patients generally stick with the health insurance plan and do not doctor shop), have begun investing significant resources into training doctors to be better communicators. Allowing patients the time to talk can lead to shorter appointments. When patient complaints are ignored or their expressions interrupted, the focus of attention is again on the care provider and the patient feels ignored.

In September 2003, a study released by the World Medical Association[28] described a fundamental shift in the patient–physician relationship away from an authoritarian paternalistic model and toward a partnership approach to care, that is, patient empowerment. The study reported that patients appeared to be more confident and empowered, while physician confidence in patient self-management remained more modest. The researchers conducted 2506 interviews with patients and 1201 interviews with primary care providers in 2002 in 6 countries—the United States, United Kingdom, Canada, Germany, South Africa, and Japan. Some of the findings included:

- All countries agreed that authoritarian paternalistic relationships between physicians and patients were on the decline; they were being replaced by mutual partnerships.
- Compared to 10 years ago, most patients believed that they asked more questions, made more choices and actively evaluated benefit-risk to a medical regimen.
- In general, issues such as compassion, trust, understanding, patience, and listening skills were more highly rated by patients than easy access to see the doctor.

In another study, Dibben and Lean[29] presented empirical research from a study of trust and cooperation between chronically ill patients and their physicians. The paper detailed models of trust and cooperative behavior designed to aid interpretative analysis. The paper presented 16 examples from interactions observed between patients and their care providers. It reported that physicians appeared to make in-clinic opportunities for building resilient trust relations with patients based on common understanding and experience, engendering more rapid patient compliance. The researchers cited significant patient empowerment and improved health-care delivery because of the compliance achieved.

However, regardless of the institutional models that have been created to address communication between care provider and patients and the studies that have shown enhanced gains in patient empowerment, one of the biggest hindrances to change may be that most training programs focus on changing doctors' behaviors, even though it takes two to create a relationship. Studies suggest that the more equal the relationship between doctors and patients, the more likely it will translate into health benefits. Physicians need to develop cultural sensitivity that will help them identify those aspects of clients' behavior that are determined by their cultural backgrounds, that is, "inflated" respect for authority that discourages dialogue. Patient passivity may be a risk factor in the treatment of diabetes. Patients need the opportunity to practice asking questions and interpreting the answers. Physicians need to adapt treatment plans and services that meet culturally unique needs since cultural competence is the thoughtful application of cultural data to practice.

The challenge to health-care practitioners is to develop sensitivity that recognizes that knowledge, understanding, and acceptance of cultural and human diversity are prerequisites for effective work with minority patients. It is an ethical obligation for physicians to develop sensitivity to cultural differences if they hope to make interventions that are consistent with the values of their patients. The physician's role is to assist patients in decision making that is congruent with the patients' worldview, not to convince patients to live by the physician's values. Unless the patient's social and cultural context is taken into consideration, it is difficult for physicians to appreciate the nature of patients' struggles with diabetes. Patients may be very slow to disclose information and have different expectations about the patient–physician interaction. Patients may come to you with varying beliefs related to social roles and identity. For example, in many cultures, a woman's identity within her family and her self-esteem are in large measure dependent on her reputation as a good cook. Plumpness is also associated with healthiness and a large appetite is regarded as normal in many cultures. Different people will place different emphases on the importance of healthy eating and even upon the importance of good health itself. A woman's culinary expertise may be at odds with the diabetic regimen recommended by her care provider for self-care as well as family care.

The awareness of the dynamics that result from cultural differences such as value preferences, perceptions of illness, health beliefs, and communication style will help practitioners adapt treatment plans that meet culturally unique needs. The integration of these factors into professional decision making may enhance patient adherence. Failure of patients to return for visits or adhere to a health-care regimen is a major barrier to the delivery of effective medical services. Disregard for patients' cultural norms often results in increased patient dissatisfaction and nonadherence. The lack of awareness of cultural issues increases social distance, breaks down communication, and precipitates misconceptions between minority patients and their care providers.

Contemporary interaction between care provider and patient originated in Euro-American culture and is grounded on a core set of values. It is a myth that these approaches are value-neutral and are applicable to all human beings. For example, some of the values implicit in most traditional interactions include an emphasis on individualism, the separate existence of the self, individuation as the foundation for maturity, and decision making and responsibility as resting with the individual rather than the family. There is a danger of imposing these values of individual choice and autonomy as being the only "right" values and as having universal applicability. In some cultures, the key values are collectivist and consider what is good for the family. Regardless of the care provider's orientation, it is crucial to listen to patients and determine how best to deliver the care they need that is appropriate for them in their cultural milieu. In interviews with compliant minority patients, they attribute their progress of adherence to a medical protocol to feelings of trust in their care provider, being understood by him/her, and the feelings engendered when they felt empowered to make informed choices on their own behalf.[13] Providing a backdrop of acceptance and support by listening and acknowledging the patient's social and cultural background often leads to negotiation and facilitation of interaction leading to adaptation of a regimen that is most likely to result in adherence.

An empathetic care provider who is also culturally competent will strive to understand patient needs and avoid forcing patients into a preconceived mold.

Health-care providers are helping patients kick bad habits and start new regimens by turning the tables on the traditional doctor–patient relationship. They are using a technique called *motivational interviewing*, which is developed and used in the 1980s in substance abuse and addiction counseling. It has since been adapted for chronic disease management, medication adherence, and weight-loss counseling by health systems including Aetna and Weight Watchers.[30] Instead of telling patients what to do and scolding them when they are not compliant, care providers ask the individual what changes he/she is willing and able to make and then promotes the patient's desire, confidence, and commitment to treatment compliance. Doctors who lecture or give scary warnings can cause patients to become defensive and disengage. When people are struggling, they don't like to be told what to do or be blamed for noncompliance. Care providers are being trained to offer choices rather than prescriptions and avoid terms such as "should," "must," and "have to." Many doctors will struggle with this approach to finding the right balance between supporting patient choice and autonomy and meeting their obligations to make informed recommendations. However, rather than push a person beyond what they think they can do, the approach aims to encourage patients to set their own minimum goals.

Ethics is an integral part of how we think about care and caring. The *respect for patient autonomy* acknowledges an individual's right to hold opinions, make choices, and take actions based on their personal values and beliefs. Autonomy provides the foundation for informed consent in which a patient fully informed about her medical condition and the available alternatives for care freely chooses to accept or decline treatment. Two conditions are essential for autonomy: (1) independence from controlling influences and (2) the ability to make choices. Although patients largely wish to be informed about their medical circumstances, many very sick, and some minority patients do not want to make their own medical decisions or even want to participate in the decision-making process. The ideal of patient autonomy is that physicians should ask their patients if they wish to receive information and make decisions or if they prefer that their families handle such matters. This position places choice in the hands of the patient.

The central doctrine in the field of bioethics and health law is that of *informed consent*. It is also an integral part of the patient-care provider relationship. Providing clients with information they need to make informed choices tends to promote the active cooperation of patients in their adherence plan. Informed consent occurs when a patient is competent to act, receives a thorough (disclosure) explanation, understands the explanation, is informed of available alternatives, acts voluntarily, and consents to the intervention. By educating patients about their rights and responsibilities, care providers enhance patient empowerment and ultimately patient adherence.

Behavior mediates almost every aspect of health and health care. Whether we focus on risk behaviors of individuals or the appropriate use of the latest biomedical technology, attention to behavior leads to better outcomes. To date, however, what is known about behavior is rarely incorporated into the planning and delivery of medical care. Behavioral interventions and treatments have largely been overlooked as cost-effective ways to identify and change health-related behaviors. There is evidence-based behavior change interventions available to address the behavioral risk factors associated with diabetes, that is, obesity, poor diet, sedentary life-style, and so on. There are effective interventions that improve diet, increase participation in diabetes screening programs, reinforce behaviors that prevent added risks for injury to the diabetic patient, and promote self-management of diabetes. Behavioral interventions can help change physician behavior, reduce stress-related visits to providers, and decrease client turnover.

Ashraf, a researcher at Harvard University contends that by understanding the cognitive processes underlying our health choices and applying the tools of behavioral economics, it is possible to design products and programs that encourage good health decisions and long-term behavioral change.[31] Finding innovative ways to overcome barriers to change requires a fundamental shift in how program designers and providers think about health care. It starts by prioritizing the end user, a novel approach in a sector where institution-level, top-down decision making is the norm. Dr. Ashraf suggests that providers and recipients can co-create health. The incentives, behavioral nudges, and other tools of psychology used by health program designers work because they make good health decisions easier and poor ones more difficult. The best programs create new habits, replacing an undesirable behavior with a beneficial one. Therefore, what the patient values and why she makes the decisions she does is so important to successful program design.

There are two things many of us have in common: We want to slim down, and we want to make money. So why not combine them? Commitment devices are contracts or other arrangements that formalize a patient's/client's pledge to achieve an objective. Researchers in a poverty action initiative[32] designed a commitment stratagem to help smokers quit and tested it in a randomized, controlled trial in the Philippines. Smokers in the program were offered a savings account in which they made deposits that could not be withdrawn for six months; at that time, if they passed a urine test for nicotine they got their money back. If they failed, the money was donated to charity. The study demonstrated that smokers in the commitment group were more likely to have quit than those in the control group. Participants in the commitment group were also more likely to pass a surprise nicotine test six months later. Monetary incentives can have powerful effects even after they are discontinued.

Economists Gary Gharness and Uri Gneezy[33] found that when you pay people to go to the gym, they are more likely to go but are also more likely to remain committed even after the payments end. By making each trip to the gym feel less costly, incentives can lead to the formation of new habits. Weight loss participants who received financial incentives were more likely to stick with a weight loss program and lost more weight than study participants who received no incentives, according to Mayo Clinic research that was presented in March, 2013 at the American College of Cardiology's 62nd Annual Scientific Session. Previous studies have shown that financial incentives help people lose weight, but this study examined a larger group of participants (100) over a longer period (1 year). One hundred healthy adult

Mayo employees or their dependents, ages 18 to 63 with a body mass index (BMI) of 30 to 39.9 kg/m^2, were assigned to one of four weight loss groups: two with financial incentives and two without. An adult who has a BMI of 30 or higher is considered obese, according the Centers for Disease Control and Prevention. All participants were given a goal of losing 4 pounds per month up to a predetermined goal weight. Participants were weighed monthly for 1 year; previous financial incentive studies followed up patients for 12 and 36 weeks. Participants in the incentive groups who met their goals received $20 per month, whereas those who failed to meet their targets paid $20 each month into a bonus pool. Participants in both incentive groups who completed the study were eligible to win the pool by lottery. Study completion rates for the incentive groups were significant compared with the nonincentive groups: 62% versus 26%. In the incentive groups, participants' mean weight loss was 9.08 pounds, compared with 2.34 pounds for the nonincentive groups.

In other financial incentives to lose weight, HealthyWage.com lets you legally wager and win money for losing 10% of your body weight, successfully taking your BMI from obese to healthy or competing in a team-based weight-loss challenge. Another financial incentive for weight loss involves declining a gym membership and opting instead to reserve and pay for gym classes in advance (i.e., SoulCycle or Barry's Bootcamp). You're less likely to skip out on your seat session when there's a financial amount attached to it.

Understanding people's motivations in the co-creation of health can yield payoffs for small investments. Bags of lentils costing just a dollar each were highly effective in inducing people to get vaccinated in India.[34] It would be short-sighted to overlook simple, inexpensive, and powerful behavioral interventions that can help close the gaps in the health-care delivery system.

If market-driven health-care systems are to survive, they must meet the demands of consumers, improve physician–patient communication, and develop interventions that enable consumers to take greater control of their health. Time-tested and proven behavioral change services and interventions directly respond to these needs and allow health-care plans to play a central role in primary prevention to reduce health-care risks. However, a knowledge gap exists between what health behavior research can do to help the health-care system achieve its goals. At the consumer level, patients are often unaware of behavioral approaches and fail to demand them from their health-care plans. Health-care providers continue to view pharmaceutical, diagnostic, and/or surgical interventions as easier, quicker, and more effective than behavioral procedures, or they do not expect or trust patients to comply with behavioral recommendations. At the organizational level, health-care plans have resisted integrating them fully into their service regimen because they remain unconvinced of their effectiveness. The bulk of health-care research continues to be focused largely on traditional medical models and/or interventions rather than on behavioral or combined biomedical/behavioral approaches. Perhaps with more scientific evidence to substantiate the need for behavioral interventions and their effectiveness, health-care systems will have more incentive to incorporate them into their health-care plans. If behavioral interventions are to be accepted more fully, health-care providers, researchers, funders of research, and health-care policy makers must all begin to address these interventions more optimistically. Specifically, the role of behavioral interventions is neither clear nor vital within a traditional medical model in which the primary goal is to offer a "cure" for an existing disease. However, in a risk management model of health care in which the goal is to prevent disease and reduce risk factors for multiple diseases, such interventions become key factors. Making comprehensive evidence-based behavioral interventions for health promotion and management available to consumers and practitioners will enhance the potential for improved health outcomes, expand patients' choices, and enhance quality of life.

SUMMARY

The changing cultural environment is increasing its insistence on a more cooperative relationship between doctor and patient with the patient taking an active and informed role. Because the disease and the person with the disease cannot be separated, it follows that psychological and medical care cannot be separated. Therefore, health-care providers and patients need to pool their expertise to pattern customized treatment plans that are suitable to the patient and his/her disease. The GDM patient faces a new diagnosis and a temporary illness mode (unless she develops type 2 diabetes) that will cease with the birth of her baby. However, the patient with pregestational diabetes is wrestling with a life-long illness in which failure to maximize glucose control may seriously compromise both her and her fetus. The physician who uses understandable language, provides constructive, culturally competent advice, and creates a humane environment enhances the likelihood of adherence. In this environment, noncompliance is viewed as a temporary rather than as a permanent lapse. Ultimately, patients control what they do with the recommendations they are given. Whether the patients follow recommendations depends not only on their understanding of what they are to do but also, and probably to a greater degree, on their judgment and feelings about the meaning those recommendations have for them and their lives. The area of doctor–patient communication that facilitates patient empowerment may offer adherence research both a practical and a theoretical framework. It may provide soundly based interventions designed to improve diabetes care, one of medicine's most pervasive problems.

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The Association Between Glucose Thresholds and Perinatal Complications

14

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Measurement is the first step that leads to control and improvement.
If you can't measure something, you can't understand it.
If you can't understand it, you can't control it.
If you can't control it, you can't improve it.

—H. James Harrington

Key Points

- *Correlated normality* is defined as desired or undesired outcome; it is commonly used as the endpoint in clinical studies.
- The *customary range of normal* refers to the same spectrum of data from a single variable (e.g., glucose) that requires different thresholds for different clinical complications.
- Approximately 80% of gestational diabetes mellitus (GDM) and only 40% to 60% of pre-existing diabetic women achieve the targeted level of glycemic control.
- Spontaneous abortion and congenital malformations are associated with relatively higher glucose thresholds; therefore, prevention is *more* attainable.
- Fetal macrosomia/large for gestational age (LGA) and metabolic complications are associated with a lower glucose profile; therefore, prevention is *less* attainable.
- Delay in lung maturation in diabetic patients is negligible in the presence of good glycemic control.
- The rate of preeclampsia is related to the severity of GDM and the level of glycemic control.

INTRODUCTION AND DEFINITION OF TERMS

This chapter examines the potential to establish different glycemic thresholds to be targeted by the care provider to decrease adverse perinatal outcome from diabetic complications. These thresholds will be compared to the normal glycemic profile when possible by both the correlated and isolated definitions of normal. Outcome variables to be evaluated: large-for-gestational-age (LGA) and small-for-gestational-age (SGA) infants, metabolic complications, lung maturation, stillbirth, spontaneous abortion, congenital anomalies, and preeclampsia.

NORMAL GLYCEMIC PROFILE IN NONDIABETIC PREGNANCY

The association between abnormal glucose and adverse pregnancy outcome has become axiomatic yet, to date, there is scant evidence on glucose data and pregnancy outcome. From 1991 to 2010, there were approximately 10,300 English language academic citations on diabetes in pregnancy. Of these, 76% were primarily editorials, letters, meta-analysis, practice guidelines, reviews, and consensus reports from development conferences; only 6% provided glycemic data on patients. However, even in these academic works, the majority did not provide pregnancy outcome based on having reached/failed to reach targeted glycemic levels, method of testing, and so on.

There is scant information on the glycemic profile of nondiabetic pregnant women. The existing studies are limited because of small sample sizes and single day testing during hospital conditions (not reflective of real-life situations).[1–4] Complicating this issue are investigators who use varying parameters when presenting levels of glycemia, that is, mean blood glucose values, premeal mean glucose, or postprandial values. Moreover, there is a wide range of testing methods from venous blood tested weekly to daily self-monitoring

capillary blood glucose. As a result, the glycemic profile in nondiabetic pregnant women is not well defined. Three studies[5–7] with relatively larger sample sizes evaluated the glycemic profile in nondiabetic pregnant women. Two of the studies used self-monitoring blood glucose throughout the third trimester, whereas one study used a continuous blood glucose measuring system. The unique features of these studies included longer duration and patients not altering their lifestyles (diet and/or activities) during the study period. Therefore, the data gleaned from these studies can provide a more accurate reference for what is the normal glycemic profile in nondiabetic women during pregnancy. In most centers, when pregnant diabetic women are attended, the targeted level of glycemia is usually based on the upper limits of normal for pregnant nondiabetic populations. Therefore, using two standard deviations (SDs) above the mean (fasting plasma <100 mg/dL and 2-hour postmeal <120 mg/dL) from scant data became the targeted level for glucose control. It is no surprise then that in some complications, these thresholds are not adequate to optimize pregnancy outcome. In light of the current data on glycemic profile in nondiabetic pregnant women, the "gold" threshold for each complication needs a definition in relation to pregnancy outcome rather than a mathematical expression of two SDs above the mean (especially since most hover around the mean and not above it) (Table 14-1).

Several investigators have chosen to report their data with glycosylated hemoglobin. Here too, the lack of uniformity among the laboratories produce results in multiple thresholds of normality (range: 4.5%–8.9%). In addition, most of the studies found poor to no correlation between glycosylated hemoglobin and mean, fasting, premeal, and postmeal blood glucose values.[8,9] On the basis of associations with adverse pregnancy outcomes, HbA1c measurement is not a useful alternative to an oral glucose tolerance test (OGTT). Overall, the association was significantly stronger with glucose measures than with A1c for birth weight, skin fold, and so on.[10] In addition, HbA1c is a retrospective measure reflecting a 10-week period prior to the actual test result. Therefore, it cannot be used in the daily management of blood glucose surveillance with its requirement for immediate therapeutic intervention. Moreover, hemoglobin A1c does not adequately represent the complexities of glycemic control in women with type 1 diabetes who are presumed to have achieved glycemic control in the first trimester of pregnancy.[11,12] However, when a retrospective evaluation of level of glycemic control is needed for both patient consultation and risk assessment, as in cases of congenital malformations, spontaneous abortion, or a known stillbirth, HbA1c becomes a useful measure (Table 14-2).

In summary, the association between glucose boundaries maximizing perinatal outcome in the pregnant diabetic woman and the normal glycemic profile in nondiabetic women can be compared. However, it should be understood that the normal values found in the nondiabetic subject are not automatically the targeted levels that should be established to prevent a complication in pregnant diabetic women. Taking the approach that the nondiabetic profile should be targeted in pregnant diabetics may result in over- or undertreatment causing iatrogenic damage. When anticipating the achievement of targeted levels of glycemic control, the success rate will be determined by the established threshold (Figure 14-1). Furthermore, the ability to achieve success in controlling blood glucose levels will be affected by method of testing, patient compliance, level of physician commitment to achieving targeted levels of control, and type of diabetes. For example, in our patient population, when targeted levels of control were defined as <105 mg/dL, only 47% of type 1 diabetic subjects achieved this level, 60% to 70% of type 2, and 80% of GDM.

The importance of achieving the established level of glycemic control in the treatment of diabetes in general, and particularly in pregnancy, is well established. The Diabetes Control and Complications Trial Research Group [13] demonstrated that vascular complications (nephropathy and retinopathy) are significantly decreased with intensified therapy. With intensive treatment, there were significant reductions in microvascular and neuropathic complications reported in type 2 diabetics in the UK Prospective Diabetes Study.[14] However, the levels designated "normal glycemia" in these studies were notably higher than targeted glycemic levels in pregnancy.

TABLE 14-1 Recommended Therapeutic Threshold in Diabetic and Nondiabetic Women

	DCCT	ACOG	ADA	4th Intl'	Canada	Non-DM
Fasting	70–120	60–90	<105	—	75	
Premeal	70–120	60–105	—	—	<95	78
Postmeal						
1 h		<130–140	<155	<140	<140	105
2 h		<120	<130	<120	<120	97
90–120 min	<180	—	—	—	—	—
2–6 AM	>65	60–90	—	—	—	68
Mean	NA	≤100	—	—	—	84

Abbreviations: ACOG, American Congress of Obstetricians and Gynecologists; DCCT, Diabetes Control and Complications Trial; DM, diabetes mellitus.

TABLE 14-2 The Association Between HbA_{1c} and Blood Glucose

SMBG	SD	HbA1c
87	–2	5.50
96	–1	6.25
105	0	7.0
114	1	7.75
123	2	8.5
132	3	9.25
141	4	10.0
150	5	10.75
159	6	11.5
168	7	12.25
177	8	13.0
186	9	13.75
195	10	14.5

Abbreviation: SMBG, self-monitoring blood glucose.

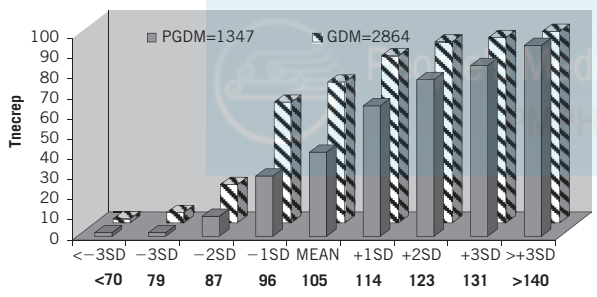

Figure 14-1 Patient frequency by level of glycemia.

DEFINING NORMAL OUTCOME

With the goal of achieving glycemic levels that maximize normal pregnancy outcome, phrases such as "tight glycemic control," "stringent glycemic control," "near normoglycemia," and "euoglycemia" have been used interchangeably. Therefore, the intended goal for defining normal outcome needs to refer to a baseline that represents the glycemic profile of nondiabetic pregnant women whose abnormal glucose levels are reduced with treatment. Nonetheless, unresolved issues remain: Is the glycemic profile similar between obese and nonobese pregnant women? How should the glycemic profile be characterized and measured?

The ranges of normal and abnormal are the foundations of medical decision making. A diagnosis is the single most important component of medical care that dictates decisions related to treatment, prognosis, and the use of health resources. A practitioner's ability to understand variations is fundamental to his/her making an accurate diagnosis for a specific disease. The terms normal/abnormal appear to be almost self-explanatory. However, the range suggested for the measurement of a specific medical condition is often unsuitable for the stated goals, and the basic concept of normality is ambiguously or inconsistently applied. In addition, the transition from normal to abnormal is continuous and reversible as in the level of glucose in a diabetic patient, which may increase or decrease from normoglycemia to hypoglycemia.

In nonpregnant diabetic women, the goal of treatment is to reduce glycosolated hemoglobin (A1c) to approximately 6% to 7%. This range represents normal fasting and postprandial glucose concentrations in the absence of hypoglycemia. In treating diabetes in pregnancy, the medical team needs to identify glycemic levels to create a treatment plan. Then, achieving the targeted level of glycemic control will be pivotal in the treatment protocol with beneficial results for type 1, type 2, and GDM.[15] Researchers need to balance the trade-off between sensitivity and specificity (finding all the true cases vs. misdiagnosis of some healthy individuals as having a disease). Particularly for laboratory tests, separation of normal from abnormal is inevitably arbitrary. As a result, there is a need to establish thresholds or boundaries for targeted glycemic levels appropriate to a specific diabetic complication.[16–19]

CORRELATED NORMALITY

There are three categories to define normal: correlated, isolated, and customary normality.[20] Correlated normality is defined as desired/undesirable outcome. For example, macrosomia versus normal size fetus; hypertension versus normal blood pressure in pregnancy in which the threshold changes in association with the desired outcome. Another example is the recent change in the diagnostic criteria for type 2 diabetes from fasting plasma glucose (FPG) of 140 to 126 mg/dL. This change was based on the association between the proposed glucose threshold and the vascular complications (nephropathy, retinopathy) that develop in diabetic patients. The definition of what is normal using the concept of correlated normality is based on what the physician and/or the patient are willing to accept as "normal." In the past, cesarean delivery was one of the classic measures of abnormal outcome in obstetrics. Today, legitimating cesarean delivery for women with previous cesarean delivery, increased rates of induction of labor, and the advocacy by both physicians and patients for women's rights to cesarean section on demand rather than for medical indications have all influenced the rate of cesarean delivery. Therefore, this endpoint *should not* be used as an outcome measure in pregnancy but rather as a measure of practice-directed medicine that is not related to the concept of correlated normality. Correlated normality is associated with an ideal or desired state of health that requires data from other variables that need to be considered simultaneously. For example, if the desired outcome is a normal-size fetus, a thorough investigation of all other known confounding variables must be concurrently analyzed using multivariate analysis. Abnormal is a current state of illness or an inability to achieve a desired level of health. Correlated normality is the traditional method for making decisions about normal/abnormal conditions.

In the definition of *isolated normality*, normal is categorized as a univariate concept, emerging from boundaries set on values of the spectrum of a single variable such as glucose values. Abnormality is then based on a statistical process such as greater than two SDs above a mean value for a population or mathematical methods such as 95th percentile. By using the isolated approach, "the rate of a condition is determined prospectively by arbitrary

assignment rather than by being based on a clinical demonstration of true dysfunction." Isolated normality often uses the normal Gaussian distribution to display boundaries of normality. Therefore, what is within the boundaries is designated "normal" and anything outside of the boundaries "abnormal" regardless of the presence/absence of disease. For example, all large and small fetuses above the 90th and below the 10th percentile are considered abnormal regardless that many of them are constitutionally large or small. Inherent in this last concept of laboratory abnormality is the view that if the disease can be identified before the specific complication develops, effective treatment could prevent, or at least delay, the onset of that complication.

The *customary range of normal* refers to the same spectrum of data from a single variable (glucose) that requires different thresholds for different clinical phenomena. Can we identify different thresholds of glucose required to prevent a given complication? In studying gestational and pregestational diabetes, values are related to the likelihood of a particular laboratory value being associated with a subsequent adverse event developing in the future, such as plasma glucose concentrations and risk of macrosomia. Therefore, there is a need to establish thresholds or boundaries for each complication to coordinate glycemic treatment and optimize perinatal outcome.

The need to support the concept of customary normality in the treatment of GDM requires that several unresolved issues be addressed: (1) definition and methods to measure glycemia; (2) level of glycemia required to optimize maternal and fetal outcome; (3) incorporation of testing frequency and glucose variability into treatment modality; (4) determination of glycemic threshold for obese/nonobese pregnant diabetic women; and (5) confounding effects such as weight gain, gestational age at initiation of therapy, and therapy modality on pregnancy outcome.

Several authoritative bodies have recommended varying levels of glycemia to be targeted in diabetes in pregnancy. The source of these recommendations utilized the concept of isolated normality based on nondiabetic profiles.[21–24] Moreover, adding to the lack of uniformity, investigators have used varying parameters when presenting level of glycemic control, that is, overall mean, postprandial mean, glycemic variability, or HbA1c.[12,25,26] The majority of studies do not distinguish between type 1, type 2, and GDM and do not refer specifically to outcome in obese and nonobese patients. There is a wide range of testing methods from venous blood tested weekly to daily self-monitoring capillary blood glucose. Two methods that measure glucose have gained popularity, the older method of self-monitoring and continuous glucose monitoring. Continuous glucose monitoring in pregestational diabetes (type 1 and type2) reveals clear differences in the level of glycemic control. Women with type 2 diabetes spend approximately 33% less time hyperglycemic throughout pregnancy than women with type 1 diabetes.[27] On the other hand, a recent randomized study comparing these two methods in pregnancy revealed a similar rate of severe hypoglycemia (approximately 16% and prevalence of LGA infants (45% vs. 34%, $P = .19$). The use of the more costly real-time continuous glucose monitoring compared to self-monitored plasma glucose seven times daily did not improve glycemic control and pregnancy outcome in women with pregestational diabetes.[28]

Some researchers report data with glycosylated hemoglobin. Here, too, the lack of standardization and consistency among laboratories has resulted in multiple thresholds of normality. The slow kinetic of glycosolated hemoglobin accumulation and physiological changes in erythrocyte formation during pregnancy means that A1c is only a limited and retrospective predictor of acute blood glucose changes. This may provide an explanation for the poor pregnancy outcomes even in women with apparently well-controlled blood glucose.[11,12,29] Patients with comparable mean glucose or HbA1c values may have strikingly different daily glucose profiles (differences in number and duration of glucose excursions). Hyperglycemia may induce oxidative stress and interfere with normal endothelial function by overproduction of reactive oxygen species. This may contribute to diabetic complications through several molecular mechanisms. Glucose variability may also influence these functions.[30,31]

GLUCOSE MARKERS FOR THE INITIATION OF PHARMACOLOGICAL THERAPY

The controversy over gestational diabetes as a clinical entity has, in the past decade, been resolved. As a result, there have been many publications of both retrospective and randomized studies[32–35] that demonstrated that untreated GDM is clearly associated with increased adverse outcome and that treatment will significantly improve pregnancy results. Needless to say, described treatments demonstrated attempts to improve glycemic levels. Furthermore, it has been confirmed that obese patients will benefit from pharmacological therapy[36] and excess weight gain in pregnancy is associated with increased adverse pregnancy outcome.[37–39]

To begin to establish the glucose thresholds required to maximize pregnancy outcome, a thorough understanding of the pathophysiology of GDM patients is paramount. Pregnancy is characterized by a hyperinsulinemic state and a decrease in insulin sensitivity. The inability of the target organ to respond to normal insulin pregnancy-induced changes contributes to the cause of GDM. A healthy β-cell will have the ability to respond and secrete sufficient insulin to offset resistance; however, impaired β-cell secretion in conjunction with insulin resistance results in GDM. Diet and exercise regimens remain the foundation for both the prevention and the treatment of women with GDM. In studying insulin characteristics using the minimal model,[40] the authors reported that a substantial number of affected patients, even after four weeks of diet therapy, failed to improve insulin secretion and sensitivity to insulin to the levels of non-GDM women.[41,42] These patients require additional pharmacological therapy to achieve the targeted level of glycemic control.

Studies of hyperinsulinemic–euglycemic clamps used a tree model for insulin resistance that included fasting glucose, insulin, age, gender, and body mass index (BMI). The results demonstrated that only fasting insulin >10.6 uU/mL was a significant determinant for being insulin resistant. This elevated insulin level was associated with FPG of >97 mg/dL in the majority of cases. These support the concept of fasting plasma >95 mg/dL as a threshold for the initiation of pharmacological therapy.[43] It is impractical and not cost effective to measure insulin sensitivity and secretion on every GDM patient. Therefore, it is necessary to identify the glucose thresholds that will require pharmacological

therapy in addition to diet therapy. In the past, FPG of ≤105 mg/dL and/or postprandial values of ≥120 mg/dL were the recommended criteria.[44–47] In our studies, we demonstrated that fasting plasma thresholds of <95 mg/dL needs to be used for insulin therapy initiation to overcome abnormal physiology. Before a care provider decides on mode of treatment, diet, or pharmacological therapy, both gestational age at initiation of treatment (to maximize the protective effect for the fetus) and the relatively short time from diagnosis to delivery (8–12 weeks) needs to be considered. This window of opportunity to alter the negative effects of the glucose abnormality is very narrow. Based on these assumptions, it was demonstrated that diet therapy prolonged for more than two weeks is not beneficial.[48] The Fourth International Workshop on Gestational Diabetes recommended FPG > 95 mg/dL and/or postprandial plasma glucose >120 mg/dL during diet therapy as the criteria for insulin initiation.[49–51] In addition, the American College recognized that lowering the FPG for insulin initiation results in a lower rate of macrosomia from GDM.[52] In summary, the maternal glycemic profile as the criteria for pharmacological therapy (insulin or glyburide) should be based on FPG of ≥95 mg/dL and when normoglycemia is not achieved.

PERINATAL MORTALITY: WHAT IS MEASURED?

A stillbirth contrasts the expectation of life with the tragedy of death. The care provider and his/her team need to address the parental issues of grief and loss while trying to provide answers to their questions about cause and chances of recurrence. Perinatal mortality remains the standard for measuring adverse outcome in pregnancy. There are more than two million intrauterine deaths defined as the demise of a fetus in the second half of pregnancy annually worldwide. Stillbirth occurs in 1 in 160 gestations in the United States, which makes it as common as infant mortality. Different definitions exist worldwide. Sweden, for example, registers all live births, irrespective of gestational age and stillbirths only after 28 completed weeks; therefore, fetal deaths before that gestational age are not included in the perinatal mortality (PNM) rate. In England and Wales, all fetal deaths between 24 and 27 completed weeks gestation, in addition to those after 28 weeks, are registered as stillbirths. This effectively changes the definition of PNM. Such variations created discrepancies in PNM rates among various countries, placing their value as a measure of perinatal care in doubt. The World Health Organization recommended that national perinatal statistics rely on weight (infants weighing at least 500 g) to avoid geographic differences. Indeed, recent analysis of PNM data in the United States by the National Vital Statistics System of the Center for Disease Control and Prevention referred to fetal deaths according to gestational age: early fetal death, 20–27 weeks gestation, and late fetal deaths >28 weeks gestation.[53] The definition is further complicated by the additional stratification of neonatal death into early and late neonatal deaths: early neonatal death is defined as the death of a live-born infant during the first 7 days after birth and late neonatal death is the death of a live-born infant after 7 days but before 29 days of birth.

Because congenital anomalies are a contributing factor in overall perinatal mortality rate, it is important to control for the effect of congenital malformations when calculating fetal and neonatal death rates. In obstetrics, observational studies account for approximately 80%, whereas randomized studies account for 11%. Studies evaluating perinatal mortality from diabetes in pregnancy are under the constraints of strict ethical standards that prevent randomized studies. Therefore, in studies that evaluate perinatal mortality, it is important that both the study and the control groups be comparable in their basic characteristics, that is, the incidence of prolapse of cord, medical complications, parity, ethnicity, prenatal care, and so on. Thus, the diseases in question, for example, GDM, types 1 or 2 diabetes become the main cause for the difference in rates between the groups for perinatal outcome.

Two recent articles addressed the causes and risk factors for stillbirth.[54,55] The articles identified the causes of stillbirth as attributable to obstetric conditions, placental abnormalities, genetic or structural anomalies, infection, hypertensive disorders, and maternal medical conditions. The authors described 4 broad stillbirth categories, 2 before and 2 after 28 weeks of gestation. The early deaths were associated with very preterm labor of a nonviable fetus when intervention would be inappropriate, that is, a group where African American women were disproportionately represented as were some specific obstetric complications: placental abruption, multiple pregnancies, rupture of membranes, preterm labor, and chorioamnionitis. Deaths after 28 weeks were associated with placental disorders, that is, insufficiency related to maternal vascular disease and, nearer term, cord complications. Also recorded were genetic and structural problems, infections, and maternal medical conditions. Relatively few term intrapartum deaths were associated with asphyxia. Black race/ethnicity, a previous stillbirth or mid-trimester loss, diabetes, drug addiction, smoking, obesity, multiple pregnancies, and single parenthood were variables that contributed to stillbirth. These factors are evident at the outset of any pregnancy; they do not define the overall burden of stillbirths into a specific group in which interventions can be targeted. As with preterm delivery, which also has numerous common denominators, risk forecasting is a very inexact science. The most probable sources of accurate information as to the cause of any stillbirth will be provided by placental histology, autopsy, and karyotyping. In the reports, a probable cause was found for more than 60% of all deaths, and this figure rose to 75% with an autopsy. In general, a growing proportion of stillbirths are being attributed to maternal, fetal, or placental causes, shrinking the proportion relegated to "idiopathic" or unexplained stillbirth. The leading causes of antepartum stillbirths were obstetric complications in 29% and placental pathology in 23%, although some of the causes of stillbirth varied significantly by race.[54] Infection as a cause of stillbirth was also less likely in whites (7%) or Hispanics (8%), compared with blacks (25%) or other races (22%). However, hispanics and whites had higher rates of umbilical cord complications as a cause of stillbirth (13% for each), compared with blacks (4%) or other races (5%). Among the clinically indicated tests for stillbirths, the placental histology identified a cause of stillbirth 52% of the time. An autopsy found a cause in 31% of cases, and karyotype testing identified a cause 9% of the time. Eight other screening tests found a cause for stillbirth in 0.4% to 4.8% of cases, depending on the test. These included screens for antibodies, toxicology, or blood glucose; tests for syphilis, parvovirus, lupus anticoagulant, or anticardiolipin antibody; or detection of fetal blood in fetal–maternal hemorrhage.[56]

Karlsson and Kjellmer[57] studied 179 women with pre-existing diabetes to evaluate the possible relationship between the degree of glycemic control (expressed as the mean daily blood glucose value) and perinatal mortality, not corrected for congenital anomalies. Patients were divided into three mean blood glucose groups: <100, 100 to 150, and >150 mg/dL. Perinatal mortality was 3.8%, 16%, and 24%, respectively. Although there is a continuous increase in perinatal mortality for the threshold used in this study, it would be clinically appropriate to use the correlated normality definition to identify the desired threshold (<100 mg/dL) that will result with the lowest rate of perinatal mortality.

Although the main cause of fetal death is metabolic acidosis, fetal hypoxia can occur in diabetes in pregnancy especially in type 1 diabetes and can be another explanation for fetal demise. In GDM and type 1 and type 2 diabetes, there are additional recognized risk factors associated with perinatal mortality, that is, diabetic vasculopathy, hypertension, and intrauterine growth restriction.[58] In both GDM and type 2 diabetes, a "triad" effect occurs that includes the relatively older pregnant mother in comparison to the gravid nondiabetic population, the higher incidence of obesity and the presence of hypertension. These patients typically exhibit elevated insulin levels, insulin resistance, and most likely suffer from metabolic syndrome. The findings of Karlsson and Kjellmer[57] on the suggested threshold associated with decreased perinatal mortality were reported in the early 1970s. Despite their findings, there were no substantial improvements in perinatal mortality. This led to the St. Vincent's Declaration in the 1990s. However, the rate of perinatal mortality remained unchanged in type 1 diabetes. Thus, decreasing mortality still remains the objective for these patients. The question then becomes whether improvement is achievable. As noted earlier, a mean blood glucose of <110 mg/dL could be obtained in approximately 40% of patients (due to the complexity and variation of their glucose metabolism). Thus, at least 60% of these patients remain with blood glucose levels that expose them to the risk of stillbirth. Therefore, it is not surprising to find national studies reporting higher perinatal mortality in these patients.[29,59–68]

O'Sullivan et al.[69] found that women with GDM have more perinatal losses than pregnant nondiabetic women (during the same time period), 64/1000 versus 15/1,000, respectively. Pettitt et al.[70] when studying 811 Pima Indian women found a direct association between a 75 g 2-hour glucose challenge test result in the third trimester and perinatal mortality. The test results were blinded from the care providers during pregnancy. Of note is that GDM women had perinatal mortality rates similar to those with pre-existing diabetes, 43–125/1000 versus 59/1,000. The stillbirths in the GDM group occurred mostly in LGA fetuses (236/1000), suggesting that maternal hyperglycemia leading to fetal hyperinsulinemia and lactic acidosis were the causes of death. Beischer et al.[71] found a higher rate of perinatal mortality in untreated GDM women in comparison to treated GDM subjects. They further suggested that reducing postprandial glucose below 140 mg/dL decreases perinatal mortality by 75%. In a previous study, these researchers[72] reported perinatal mortality rates of 3.2% and 2.8% in women whose OGTT results were above the 95th percentile (hyperglycemia) and below the 5th percentile (hypoglycemia), respectively, and only 0.6% between the 5th and 95th percentiles. Schmidt et al.[73] when comparing gestational diabetic women to the general population found a relative risk of 3.1 and 95% confidence interval 1.4 to 6.5 for perinatal death. We, in a large cohort study of 4757 GDM and 10,804 nondiabetic gravids, evaluated the rate of perinatal mortality.[74] Seventy-nine percent of the study population achieved targeted levels of glycemic control (<105 mg/dL). The incidence of stillbirth was 4.8/1000 for the GDM and 4.2/1000 for the nondiabetic subjects. The rate of neonatal death was 5.2/1000 and 5.3/1000, respectively. Our data suggest that achievement of targeted levels of glycemic control will reduce the perinatal mortality to rates comparable to the general population. We reported similar rates of perinatal mortality in 1994 when we compared intensified and conventional management approaches to GDM.[15]In contrast, perinatal mortality in pre-existing diabetes was higher than in our GDM patients but with similar rates between type 1 (stillbirth: 12/1000; neonatal death: 8/1000) and type 2 diabetes (stillbirth: 13/1000; neonatal death: 5/1000). The higher rate of perinatal mortality found in pre-existing diabetes is attributable in part to the lower rate of patients achieving targeted levels of glycemic control and to the higher incidence of congenital malformations and vascular complications. However, this study demonstrates again the relative protective effect of controlling the abnormal levels of glycemia.[74] Finally, Mondestin et al.[75] reported a 2- to 4-fold higher risk for fetal death when comparing over 10 million nondiabetic to 271,000 diabetic patients during the years 1995 to 1997 in the United States. The relative risk for fetal death increased significantly as fetal weight increased (from 2500 g to >5000 g in 250 g increments).

The data suggest that both gestational and pre-existing diabetes are associated with increased perinatal mortality when established levels of glycemia are not realized. Since a much higher rate of GDM patients can achieve and maintain the desired level of control (over 80%), it is not surprising that even in large-scale studies, the perinatal mortality rates for pregestational and gestational women are not comparable. Although several factors may influence the perinatal mortality rate, it appears that a threshold of mean blood glucose <110 mg/dL will be a major contributor for the prevention of this complication.

SPONTANEOUS ABORTION

The risk of spontaneous abortion in women with type 1 and type 2 diabetes is substantially higher than in the general population.[76–83] Only in the case of complications related to organogenesis is glycosolated hemoglobin a useful index of glucose control and predictor for the risk of spontaneous abortion and congenital anomalies. Since 50% of pregnancies are unplanned and the first pregnancy visit often occurs anytime within the first trimester, a retrospective measure of the level of glycemic control can provide a prognostic measure of quality control in counseling patients in the first trimester regarding abortion risk and congenital anomalies. HbA1c provides levels of glycemia up to 10 to 12 weeks prior to the initial measurement. The association between HbA1c and mean blood glucose level can be calculated (mean blood glucose [MBG] = %HbA1 × 33.3–86). For the sake of simplicity, any increase or decrease of 1% HbA1c translates to approximately 30 mg/dL mean blood glucose.

In the studies reporting rates of spontaneous abortion,[84–87] the mean HbA1C values averaged 10%–12% and represented

five to seven SDs above the normal mean (mean < 5%).[65] HbA1C thresholds for increased risk for abortion in the above studies were far greater than three SDs above the mean as the upper limits of normal recommended by the American Diabetes Association (ADA) position statement. This suggests that the true threshold to decrease the risk of abortion is beyond the recommended three SDs, and using the correlated normality definition would be more accurate. The HbA1c threshold associated with spontaneous abortion translates to mean blood glucose ranges between 150 and 247 mg/dL. This is an example of the clinical usefulness of the definition of correlated normality that addresses desired outcome rather than a mathematical distribution used in isolated normality.

CONGENITAL ANOMALIES

Congenital anomalies are the main cause of fetal death in pre-existing diabetes. However, studies reporting preconception care including glucose control by either self-monitoring blood glucose or HbA1C have suggested a rate of anomalies in pre-existing diabetes similar to that of the general population.[81,82,88–92] Therefore, if this is the case, congenital anomalies in this group of patients is no longer the main cause of perinatal mortality. On the other hand, others have reported that overall, achieving a rate of anomalies in pre-existing diabetes comparable to that of nondiabetic subjects is an elusive task. They refer to the fact that only 40% to 60% of these patients are below the threshold required to prevent anomalies and 50% of the pregnancies are unplanned and, therefore, recognized for the first time at six to eight weeks (almost beyond the organogenesis period). Thus, although in small sample size studies in centers of excellence the rate of anomalies can be significantly decreased when patients are provided with preconception care, this is not the case on a large scale.[81,82,89,90,92–94] The evaluation method of glycemic control was HbA1C, mean blood glucose, fasting blood glucose, mean premeal, or mean postprandial depending on the study.[81,82,89–93] In the studies using HbA1C, the threshold ranged from six to nine SDs above the mean, which translates to mean blood glucose between 150 and 168 mg/dL.[82,88,89] Studies using glucose profile (level of glycemia) to define the threshold for anomalies suggested FPG of <120 mg/dL,[90,94] postprandial of <140 mg/dL,[82,90] and overall mean <110 mg/dL.[89] In these studies, the preconception rate of anomalies was 1% to 1.5%, and in patients above these thresholds, the rate of anomalies ranged from 6% to 12%. These glucose profile thresholds suggest that prevention of anomalies is attainable since the level of glycemia required for prevention of anomalies in type 1 and type 2 diabetes is significantly higher than the glycemic profile in nondiabetic patients. Thus, the threshold for prevention can be achieved in over 80% of pre-existing diabetic patients. Finally, as reflected in these studies (Table 14-3), the difference between glucose characteristics in thresholds that prevent anomalies to glucose characteristics above these thresholds is relatively small (e.g., postprandial 136–143 mg/dL vs. 142–163 mg/dL, respectively). Therefore, these thresholds are examples of correlated normality rather than isolated normality.

DEVIANT FETAL GROWTH: MACROSOMIA AND GROWTH-RESTRICTED FETUSES

A major paradox for investigators has been their inability to decrease the rate of macrosomia to the rate in the general population, while the rate of congenital malformations has been successfully decreased during this same timeframe with preconception counseling and glucose control. In the general nondiabetic population, using the concept of isolated normality, the rate of LGA infants (>90th percentile) is 10%. Similarly, the rate of SGA infants (<10% percentile) is also, by definition, 10% based on growth standards for a given population as is the rate of macrosomia based on fetal weight (≥4000 g; 8%–10%). However, this approach does not distinguish between fetuses having diabetic fetopathy and those who are large/small (constitutional) based on mathematical locations on the statistical curve yet not marked by diabetic fetopathy. In the past three decades, the majority of studies reported rates of LGA and macrosomia of 15% to 35% and 10% to 20%, respectively,[95,84–87] in GDM and type 1 and type 2 diabetes.[8,96–98]

The ability of a study to detect a positive association or no relationship between neonatal size and level of maternal glycemic control will be affected by the inclusion/exclusion criteria for confounding variables. Therefore, analysis of the association between levels of glycemia and fetal macrosomia need to address variables such as (1) gestational age at initiation of therapy (irreversible fetopathy), (2) threshold glucose values used to initiate specific interventions, (3) method of intervention (diet/pharmacological), (4) glucose threshold targeted to forestall complications, (5) frequency and timing of blood glucose measurements,

TABLE 14-3 Glucose Thresholds and Fetal Anomalies

	Blood Glucose	Anomalies	Blood Glucose	Anomalies
Fuhrman et al.[89] 1983–84 (*n* = 292)	Mean 95	0.8%	133	7.5%
Schafer-Graf et al. 2000 (*n* = 44)	Fasting < 115	0.0%	141	One organ
			166	Multiple organ
Kitzmiller et al.[90] 1991 (*n* = 84)	Fasting 105–120	1.2%	115–134	10.9%
	Postmeal 136–143		142–163	

(6) methods of glucose measurement (self-monitoring blood glucose technique, HbA1C, laboratory), and (7) verification of glucose data used in the studies.[99] The majority of researchers have reported a relatively high rate of LGA and macrosomia in type 1 and type 2 diabetes,[100–102] whereas others have reported rates of macrosomia and LGA similar to those in the general population after subjects achieved the targeted levels of glycemic control.[103] Landon et al.[104] reported an LGA rate of 9.3% with a mean blood glucose <110 mg/dL in 43 patients with well-controlled type 1 diabetes. With mean blood glucose levels >126 mg/dl in 32 patients, the LGA rate was 34%. Roversi et al[105] in 199 well-controlled subjects (verified mean blood glucose of 80 mg/dL) reported a 3.4% rate of macrosomia. We found an LGA rate in pre-existing diabetic women comparable to the rate in the general population (10%) when the mean self-monitoring blood glucose was within one to two SDs below the mean of nondiabetic pregnant women. This corresponds to mean blood glucose of 90–95 mg/dL.[15] In a series of studies on gestational diabetic women, we demonstrated that two boundaries of glycemic control exist for deviant fetal growth in GDM women. When the mean blood glucose dips below the lower boundary (overtreating), the incidence of growth-restricted infants increases significantly. When the blood glucose levels exceeded the upper limits, the rate of LGA infants increased two- to threefold. The threshold for the upper boundary was found to be, based on cluster analysis, ≥105 mg/dL.[8] In a follow-up study, we identified that a threshold of <87 mg/dL is associated with an increased risk for SGA and a threshold of ≥105 mg/dL is associated with an increased risk for LGA infants.[97] In a large-scale study of over 2500 gestational diabetic women, these findings were reconfirmed. Using logistic regression analysis, we identified the risk factors for LGA and growth-restricted fetuses and the increased risk for deviant fetal growth in relation to increase/decrease in level of glycemia[106] (Figure 14-2).

Based on current data in the literature, the threshold for the prevention of large infants is much lower than, for example, the threshold for the prevention of congenital anomalies. The threshold for the prevention of LGA and fetal macrosomia appears to be at a level of the mean to one SD below the mean (mean blood glucose <100 mg/dL). Thus, it is not surprising that researchers report normal rate of congenital anomalies (mean blood glucose <140 mg/dL) but a high rate of fetal macrosomia. In addition, although level of glycemia is a main contributor to deviant fetal growth, other metabolic fuels such as lipids and amino acids and confounding variables affect fetal growth. Since more than half of type 1 diabetic patients are beyond the range for prevention of fetal macrosomia, it is not surprising to find many studies reporting rates of 15% to 30%. Only stratification of patients by level of glycemic control enables us to identify the glucose threshold associated with this complication.

The fetal pancreas at term is more mature and has adequate reserves to maintain fetal glucose and insulin levels not seen in the preterm fetus. On the other hand, the mission to preclude macrosomia in gestational diabetes is an achievable one since the majority of these patients can reach a glycemic profile below the threshold needed to prevent macrosomia. Failure to achieve this goal in GDM will be a result of lack of control for confounding variables and failure in the management approach. In summary, a narrow threshold ranging between 87 and 105 mg/dL should be targeted for the prevention of deviant fetal growth. The recommended targeted mean blood glucose should be approximately 95 mg/dL in management of the pregnant diabetic woman.

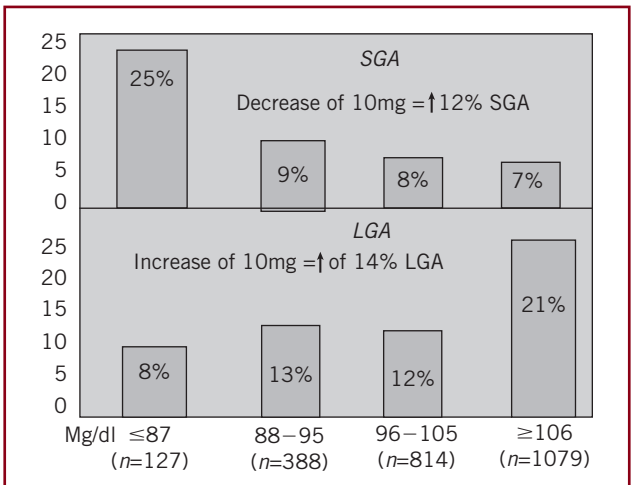

Figure 14-2 Growth diversity stratified by SMBG (n = 2408).

THE OGTT AND GROWTH-RESTRICTED FETUSES

The association between fetal macrosomia and GDM has been well documented. In contrast, the link between fetal growth restriction and glucose tolerance is less recognized as cause and effect. Early identification of growth-restricted fetuses remains a key factor in effecting the most favorable outcome. Previous works have shown that antenatal factors (i.e., hypertensive disorders, maternal smoking during pregnancy, antenatal steroid exposure, and intrauterine growth retardation (IUGR) condition) as well as poor caloric intake and/or a variety of postnatal illness episodes (i.e., severe intra-ventricular hemorrhage [IVH], necrotizing enterocolitis [NEC]) are associated with suboptimal intrauterine and postnatal growth. Recently, it was demonstrated that intrauterine inflammation plays a role in fetal growth restriction.[107–109] Although multiple risk factors are cited as possible causes for intrauterine growth restriction, the diabetic-related metabolic causes of this condition have not yet been established.[107–109]

There is scant data addressing the association between growth-restricted fetuses (SGA) and the glucose metabolism (OGTT results). The association between the lower threshold of the OGTT and growth-restricted fetuses has been reported by several investigators.[110–113] However, the relationship among counterregulatory hormones (human placental lactogen [HPL]), insulin, and glucose has not yet been fully defined and represents an important research priority. We, in a prospective study[114] of 43 fetuses at risk for growth restriction, identified three groups. Group 1 contained normotensive mothers with SGA infants. These mothers were characterized by low plasma glucose and insulin levels but normal HPL level. Group 2 consisted of hypertensive mothers with SGA infants. In this group, the plasma glucose and insulin levels were normal, but the HPL level was lower than the norm. Group 3 contained mothers with infants approximate for gestational age. In this group, the plasma glucose, HPL, and insulin were within the normal

range. We further developed a glucose index and found that a threshold of <105 mg/dL may provide a marker for identifying SGA infants of normotensive mothers (93% sensitivity, 91% specificity, positive and negative predictive values 86% and 95%, respectively). There is an apparent link between normotensive nondiabetic pregnant women and relative maternal hypoglycemia, hypoinsulinemia, and SGA infants. In addition, a "flat" OGTT needs to be interpreted as a possible abnormal pattern during pregnancy since it is associated with a 20-fold increase for intrauterine growth restriction in normotensive women. These patients need to be enrolled in fetal diagnostic units for surveillance of potential deviant fetal growth.

In a follow-up study, we compared the maternal and fetal glucose/insulin responses in gravids with/without risk factors for growth restriction. We reconfirmed that maternal glucose metabolism is associated with delayed fetal growth; however, the fetal glucose response was not altered.[115] Our findings regarding glucose and insulin in the fetal compartment are in agreement with those of Delmis et al.[116] who found no significant differences in cord blood glucose or insulin between normal-sized and growth-restricted infants. However, our results differed from those of Economides et al. and others.[117–119]

These investigators reported decreased fetal insulin, glucose, and insulin/glucose ratios at the time of cordocentesis in infants with abdominal circumference measurements below the fifth percentile. These studies, performed at earlier gestational ages, contrast ours done late in the third trimester.

METABOLIC COMPLICATIONS

Socrates alleged that the beginning of wisdom is the definition of terms. The rate of a given complication is ultimately affected by the definition of that condition. The actual rate of a metabolic complication is based on the concept of correlated normality; it is directly dependent on the threshold selected for that complication. For example, in the case of neonatal hypoglycemia, different definitions are in use from the arbitrary subjective administration of intravenous glucose to the neonate with/without neonatal testing to different levels of glycemia ranging from 45 to 25 mg/dL. Moreover, the varying modes of maternal glucose measurement contribute pitfalls to the rate of fetal complications.[120] Metabolic complications are a consequence of fetal hyperinsulinemia. The abnormal maternal glucose level causes cellular hyperplasia and hypertrophy of most fetal tissues resulting in fetal hyperinsulinemia (Table 14-4). Fetal hyperinsulinemia is a common denominator for fetal macrosomia, respiratory, and metabolic complications. Therefore, we can speculate that a similar threshold will positively affect treatment outcome in all. Jovanovic et al.[103] in studying 52 type 1 diabetic women who had achieved the established glycosylated hemoglobin levels reported the same incidence of neonatal complications as those patients in the nondiabetic matched control group. Karlsson and Kjellmer[57] demonstrated that when mean blood glucose was <110 mg/dL, metabolic complications could be reduced to rates reported in the nondiabetic population. The study by Landon[104] demonstrated that well-controlled type 1 diabetic women (mean blood glucose <110 mg/dL) had significantly less hypoglycemia and respiratory distress than those of poorly controlled women. We found similar findings in 1145 GDM women.[15] We demonstrated that with a threshold of mean blood glucose <100 mg/dL, the metabolic complication rate is similar to that of the nondiabetic population; a threshold beyond this level increases the rate and the risks[121] (Figure 14-3).

RESPIRATORY COMPLICATIONS

There is general agreement that fetal lung maturation is delayed in the diabetic fetus most likely mediated by the fetal hyperinsulinemia. Even when infants were matched by gestational week of pregnancy, infants of diabetic mothers were more than 20 times more likely to have respiratory distress syndrome than an infant from a normal pregnancy. Several investigators have suggested that maternal hyperglycemia delays fetal lung maturation.[122–124]

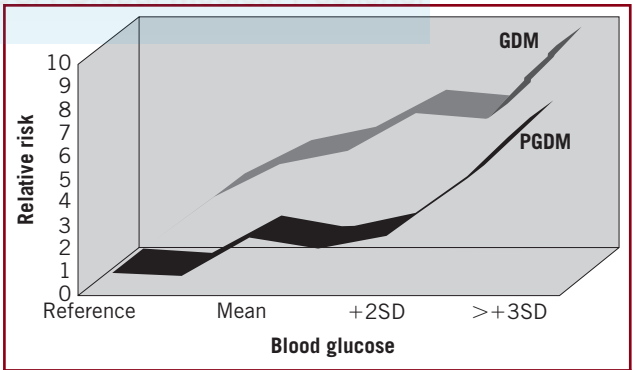

Figure 14-3 Neonatal metabolic complication.

TABLE 14-4 Type 1: Metabolic Complications in Diabetic Women

	>99	<100	RR	95% CI
Polycythemia	18.5%	4.2%	5.3	1.6–1.8
Hyperbilirubinemia	28.2%	13.8%	3.4	1.9–5.9
Hypocalcaemia	10.7%	3.4%	3.7	1.5–9.3
Hypoglycemia	36.4%	20.3%	3.9	2.3–6.7
RDS	29.8%	13.3%	2.9	1.6–4.7

Abbreviations: CI, confidence interval; RDS, respiratory distress syndrome; RR, relative risk.

Moore, in a case-controlled study, reported that fetal pulmonary maturation is delayed in diabetic pregnancy by 1 to 1.5 weeks. This delay appears to be associated with an early and sustained elevation in amniotic fluid phosphalidylinositol (PI) levels at 32 to 34 weeks.[125] Others have been unable to demonstrate any significant difference.[126,127] We found in several studies that a threshold ≥105 mg/dL will result in immature lung test results in approximately 35% of the patients. However, after 37 weeks gestation, none of these infants exhibited respiratory clinical complications.[122–124] Similar findings were found by Landon et al. in type 1 patients.[104] However, only a few studies have distinguished between pre-existing and gestational diabetic patients. As previously mentioned, since type 1 patients are less likely to achieve the established levels of glycemic control, they are at a higher risk for developing fetal lung complications. Diabetic patients who achieve a level of glucose control ≤105 mg/dL after the 37th week of gestation are at the same risk for having abnormal lung testing results and complications as the nondiabetic patients. The routine use of amniocentesis for fetal lung maturity testing is not indicated in diabetic patients that are in good glycemic control (Figure 14-4).

PREECLAMPSIA

Hypertensive disorders including preclampsia have for decades been associated with diabetes in pregnancy. Several studies have reported an increased risk for hypertension and preeclampsia,[128,129] whereas others have disputed this relationship.[130] Studies have reported a relationship between the glucose tolerance test and blood pressure.[131–133]

One study demonstrated a linear relationship between progressive glucose intolerance and blood pressure during the third trimester, which occurred even with normotensive women.[134] Furthermore, even within the normal ranges of the glucose challenge test, there was a positive correlation with preeclampsia. Women with GDM were found to be at an increased risk for hypertensive disorders.[135]

It has been suggested that insulin resistance precedes the clinical onset of hypertension in pregnancy.[136] We demonstrated the association between hyperinsulinemia and chronic hypertension in pregnancy. However, we failed to find an association with preeclampsia.[137,138] In another study of 1813 GDM women, we evaluated the relationship between level of glycemic control and the incidence of preeclampsia.[139] We found that the rate of preeclampsia was 7.8% for patients with FPG of <105 mg/dL and 13.8% for patients with fasting plasma >105 mg/dL. These results demonstrate a twofold increase for patients with more severe GDM. Moreover, for the well-controlled patients (mean blood glucose <95 mg/dL), similar rates of preeclampsia were found in all GDM severity groups. In contrast, in poorly controlled patients, there was a 2.5-fold increase in the rate of preeclampsia in the more severe GDM group (fasting plasma >115 mg/dL). The rate of preeclampsia is influenced by the severity of GDM and prepregnancy BMI. Optimizing glucose control during pregnancy may decrease the rate of preeclampsia, even in those women with greater GDM severity (Figures 14-5 and 14-6).

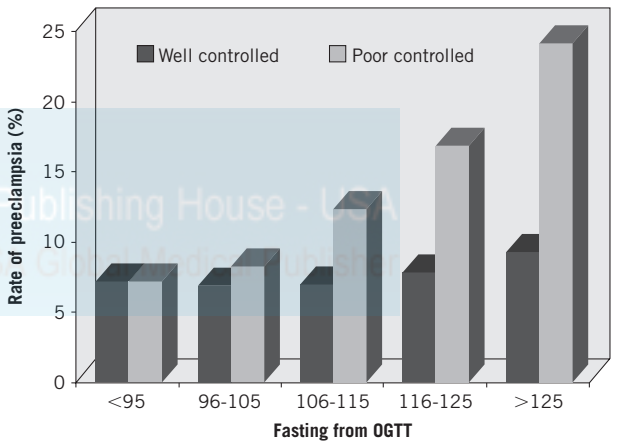

Figure14-5 Poor versus well-controlled patients. PET rate: 16% versus 6.8%; odds ratio: 2.13; 95% CI: 1.3–3.5.

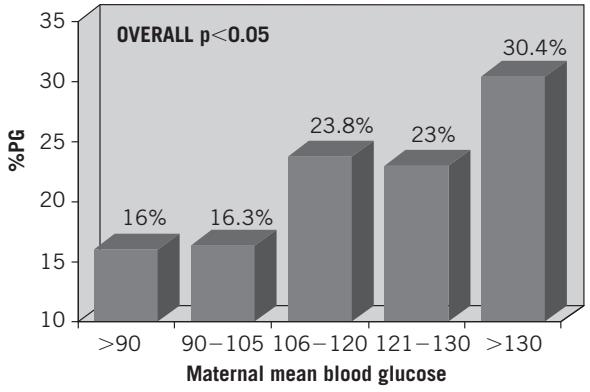

Figure 14-4 The association between level of glycemic and mature PG at 36-39.9 weeks.

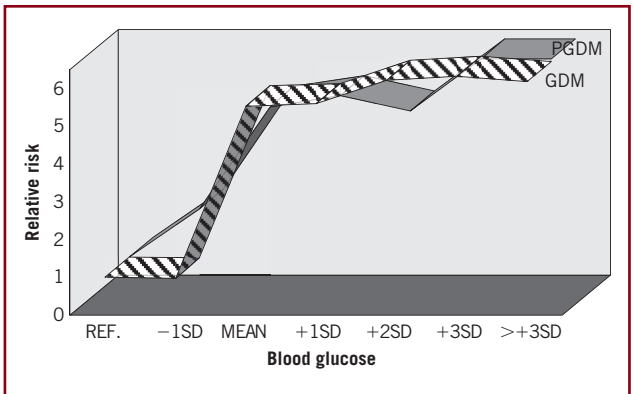

Figure 14-6 Neonatal composite outcome. (Modified from Langer.[18])

SUMMARY

Glucose is best described as a continuous variable. Therefore, the risk to the fetus increases continually in relation to the increased level of maternal glycemia up to a level to which glucose toxicity reaches its maximum effect. In the majority of cases, such as macrosomia, metabolic complications, respiratory complications, and so on (Figure 14-5), the rate will generally hover around 30% or three- to fourfold increased risk for a given complication. It is not possible to identify the exact threshold of glycemia that will make an absolute demarcation between the normal and the compromised fetus. However, it is possible to identify a glucose threshold for the majority of fetuses at risk. Although some high- and low-risk fetuses will be missed at the outlying end of the threshold, the threshold provides a guideline for the practitioner that helps maximize the potential for enhanced perinatal outcome.

Despite the common recommendations of fixed criteria for glucose control, the reader needs to remember that achieving different glucose thresholds will diminish the rates for different complications. Therefore, any improvement in the abnormal diabetic profile in the patient may be beneficial. The threshold that will decrease the rate of fetal anomalies will not decrease the macrosomia rate. Understanding this concept explains several "paradoxes" in the literature regarding infant morbidity of the diabetic mother as well as the lack of uniformity in study design that limits comparison. Finally, alteration toward improving glycemic control is always more beneficial than maintaining a questionable status quo with the admonition that "…a man's reach should exceed his grasp, or what's a heaven for?"— *Robert Browning*.

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Medical Nutrition Therapy

15

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There is no love sincerer than the love of food.

—George Bernard Shaw

Key Points

- Medical nutrition therapy has a very important function unique to maternal diabetes; it must assure adequate nourishment to the developing fetus without risking significant and prolonged maternal hyperglycemia or hypoglycemia.
- Medical nutrition therapy must also avoid overnourishment and undernourishment of the developing fetus as these may predispose the fetus to childhood and adult metabolic and cardiovascular morbidities.
- Evidence-based experiential approaches that base nutritional adjustments on episodic or continuous monitored blood glucose, weight, and ketones provide the best opportunity to achieve metabolic targets.
- Educating the patient, providing self-care skills, and adoption of a multidisciplinary approach that addresses behavioral changes are elements of a comprehensive, patient-centered approach.

Medical nutrition therapy (MNT) refers to the balance between energy input and energy output. Although it principally focuses on food planning, in recent years, it has encompassed physical activities (which will be discussed in Chapter 17, devoted to exercise and pregnancy). MNT, as all therapies, has a behavioral component as well. Pregnancy uncomplicated by diabetes presents substantial challenges. Normal pregnancy is a state of insulin resistance and accelerated insulin delivery in which maternal blood glucose levels are reduced by approximately 20% (see Figure 15-1), reflecting the shunting of nutrients from the mother to the developing fetus. To maintain glucose homeostasis and assure adequate maternal and fetal nourishment, while avoiding both undernutrition and overnutrition, maternal nutrient intake requires balancing of amino acids, omega-3 fatty acids, folic acid, iron, copper, and other minerals as well as carbohydrates, fat, and protein to assure adequate weight gain for the developing fetus.[1] Recent evidence suggests that the stability of the early in utero nutritional environment is associated with "alterations" in the fetal genome.[2] Some investigators believe that the so-called fetal origin hypothesis "suggests that the fetal hormonal and nutritional environment has an impact on future physiology and metabolism" of the child and adult. Activity and planned exercise are generally continued at the same level of intensity as the prepregnancy level unless an intercurrent event suggests otherwise.[3] In fact, there is emerging evidence that exercise may be both preventative in developing glucose intolerance in pregnancy and beneficial if gestational diabetes develops.[4]

Pregnancy complicated by diabetes presents altogether unique circumstances. Type 1 diabetes, type 2 diabetes, and gestational diabetes mellitus (GDM) constitute similar medical challenges: to maintain near normal (see Figure 15-1) blood glucose levels while assuring appropriate fetal growth and development. Diabetes in pregnancy requires that adequate weight gain occurs to promote fetal growth while addressing a physiological state that risks sudden and sustained hypo- and/or hyperglycemia. Simultaneously, the nutrient intake must be synchronized with the antidiabetic medications, which are required in the majority of women with diabetes in pregnancy to prevent dysglycemia. If the goal is to achieve blood glucose levels that mimic normal diurnal glycemic patterns of pregnancy to prevent adverse perinatal outcomes, the selection of an appropriate food plan becomes a matter of considering myriad elements: fetal growth and development, maternal nutrition, and the pharmacodynamics of antihyperglycemic medications.

There are many similarities that follow general nutritional principals in terms of MNT for pregestational and gestational diabetes. In this section, MNT is discussed from two perspectives: common approaches and clinical strategies specific to special circumstances. The overall approach is to incorporate recent research findings with practical applications to reduce variability and build consensus around nutrition management. A key element of this approach is the direct involvement of the patient. Education and skills development in self-care as well as participation in clinical decisions are hallmarks of patient-centered MNT. Without an understanding of the self-management responsibilities of the patient, MNT is substantially compromised.

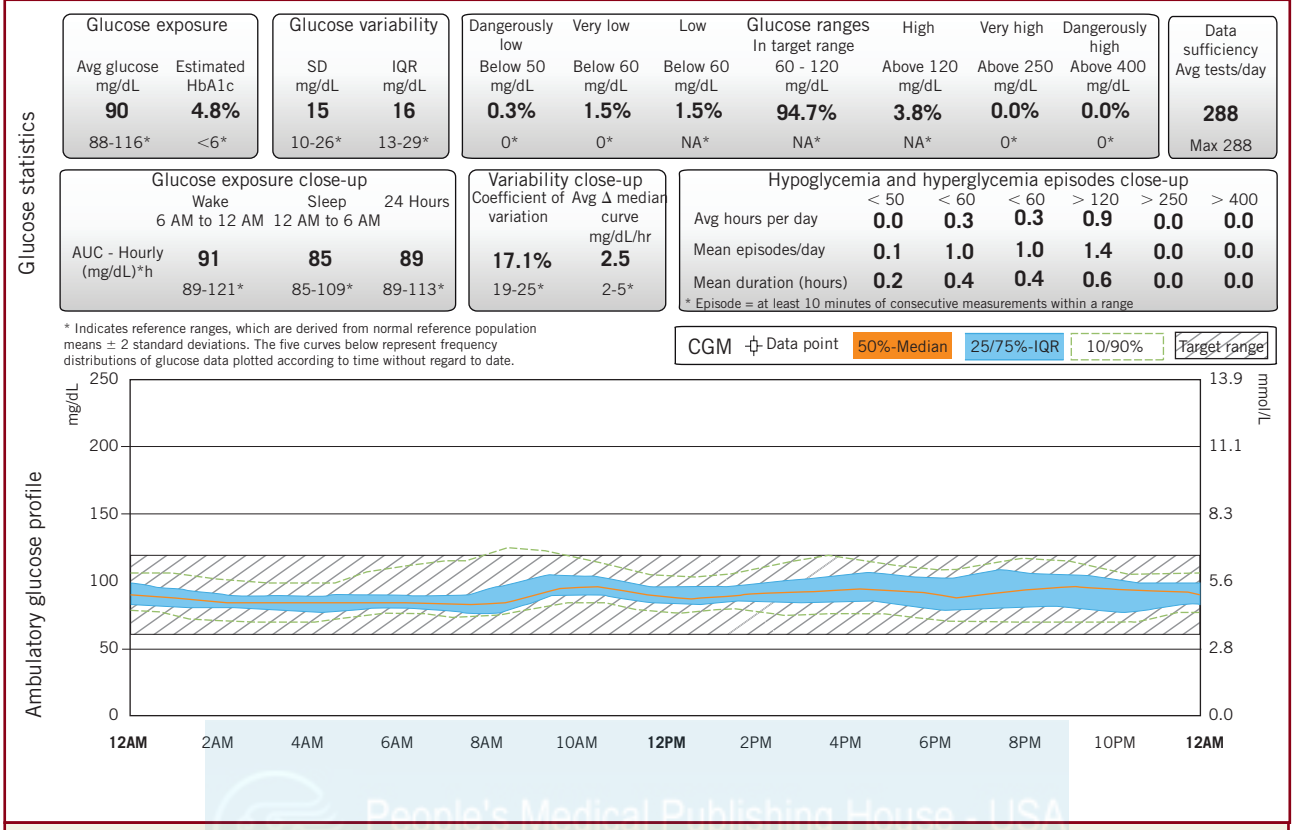


Figure 15-1 AGP of subject with normal OGTT. From a pregnant individual with normal glucose tolerance. Fourteen days of CGM, data are collapsed and graphed by time without regards to date. The five curves represent (from top to bottom) the 90th, 75th, 50th, 25th, and 10th frequency percentiles. The 50th percentile is equivalent to the median, and the area between the 25th and 75th percentiles represents the interquartile range (IQR). The area under the median (AUC) represents glucose exposure. The median also serves to measure the amount of average hourly change (CMC) in glucose level—a measure of stability. AGP rapidly identifies the period of hypoglycemia, its average number of episodes each day, and their duration.

COMMON ELEMENTS OF MNT

There is little difference between women with dysglycemia and women with normal glycemia with respect to the recommended dietary allowance (RDA) for pregnancy as published by the US Food and Nutrition Board of the National Academy of Sciences.[5] In addition, women with diabetes do not differ in terms of the need to add sufficient caloric intake to assure appropriate fetal and maternal nourishment. Acknowledging that the goal of treatment is to restore normoglycemia in pregnancy, the American College of Obstetricians and Gynecologists in its 2013 Practice Bulletin made the following recommendations[6]:

- "nutritional counseling for all patients with GDM by a registered dietician, if possible, with a personalized nutrition plan based on the individual's body mass index"; and where this is not possible, nutritional counseling by the physician;
- "carbohydrate intake should be limited to 33–40% of calories, with the remaining calories divided between protein (20%) and fat (40%)";
- "complex carbohydrates may be preferred to simple carbohydrates because they are less likely to produce significant postprandial hyperglycemia";
- "three meals and two to three snacks are recommended to distribute glucose intake and to reduce postprandial glucose fluctuations"; and
- "a moderate exercise program."

The American Diabetes Association and the National Academy of Science promulgated their recommendations for weight gain in pregnancy in 2006 and since then have reiterated these guidelines in their most recent publications.[7] Using pregravid body mass index (BMI), underweight individuals with a BMI < 19.8 kg/m^2 are expected to gain up to 40 lbs (18.2 kg) at a caloric intake rate of 40 kcal/kg/d, whereas normal weight (BMI 19.8–26.0 kg/m^2) and overweight (BMI 26.0 kg/m^2) pregnant women are expected to gain up to 35 and 25 lbs, respectively, at rates of 30 and 24 kcal/kg/d. Since it is likely that there is some weight gained prior to the first prenatal visit, weight gained between conception and the first prenatal visit is included in the calculation of total weight gain in pregnancy. This approach estimates that approximately 4 lbs of weight gain occurs during the first trimester, and subsequent weight gain is evenly distributed (approximately 1 lb/wk) during the remainder of pregnancy.[8]

Whether women are treated by MNT alone or in combination with pharmacologic agents, the distribution of nutrients is essentially the same. The only difference is that if MNT is combined with antihyperglycemic agents, dietary adjustments to synchronize with the pharmacologic treatment are considered at initiation of therapy.[9] The precise nature of nutritional interventions is controversial, whether as a stand-alone treatment or in combination with pharmacologic agents. Evidence linking moderate or low carbohydrate diets with improved glycemic control is equivocal.[10,11] This has led to the 2012 recommendations of the American Diabetes Association to conclude that MNT be "individualized" in pregnancy, in addition to considering an adjustment for ethnicity and socioeconomic status.[12]

AN EVIDENCE-BASED EXPERIENTIAL APPROACH TO TREATMENT

Since the impact of a food and activity plan can be readily measured by changes in weight (both gain and loss), diurnal glucose patterns, and ketones, an evidence-based experiential approach employs three parameters for clinical decision making.[13] Specifically, decisions concerning starting and adjusting MNT are based on (1) overnight and daytime blood glucose patterns especially related to periods of severe hypoglycemia (<50 mg/dL) and persistent hyperglycemia (>140 mg/dL lasting more than two hours) obtained from SMBG or CGM (Figure 15-2); (2) changes in weight especially during the second and third trimesters; and (3) the presence of ketones especially with hypo- or hyperglycemia. This approach requires patients to monitor their blood glucose multiple times throughout the day (including before and after each meal and at bedtime) as well as overnight and also daily monitoring of ketones and weekly measurement of weight.

Changes in caloric intake are based on maintaining blood glucose within preset parameters (60–120 mg/dL), preventing ketosis and avoiding excess weight gain.

APPORTIONING CARBOHYDRATES, FAT, PROTEIN, AND FIBER

Dietary recommendations for carbohydrates extend from 33% to 40% of total nutrient intake, with fat ranging from 30% to 40% and protein generally less than 20%.[6,14] These large variations represent a lack of consensus as to the most effective nutritional intervention that mimics normal glycemic control while assuring adequate nutrition. This is especially critical with respect to carbohydrates. The variation in recommendations of the proportion of carbohydrates needed to establish and mimic normal diurnal glucose patterns in pregnancy complicated by diabetes reflects

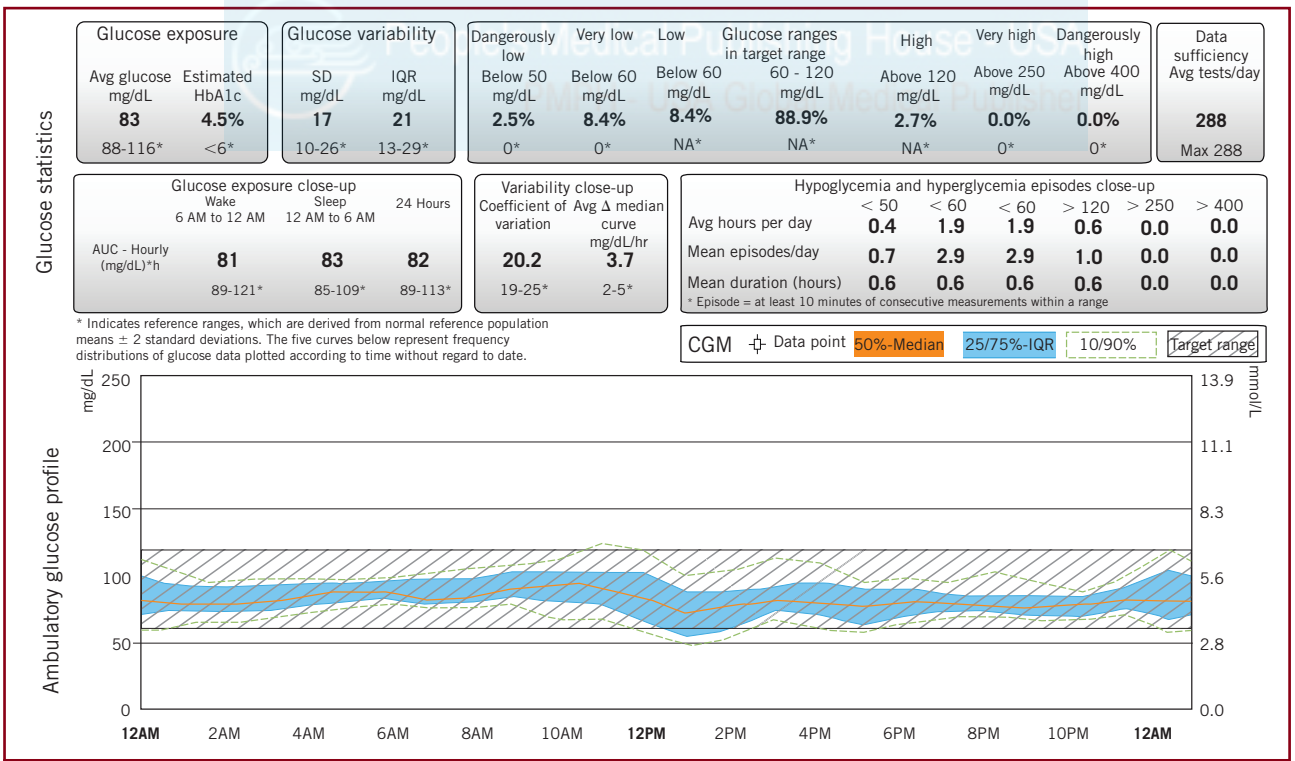


Figure 15-2 Ambulatory glucose profile report of woman with GDM at 29-week gestational age representing 2 weeks of CGM data. This report illustrates the diurnal glucose profile consisting of approximately 4361 CGM readings competed during a period of 2 weeks while treated with glyburide. As the report indicates, the mean glucose for this period was 83 ± 17 mg/dL with 89% of the glucose values within the target range of 60 to 120 mg/dL. The glucose exposure (AUC) was 82 mg/dL × hr which is 20% below the average exposure for nonpregnant women with normal metabolism.

the differences in interpretation of the postprandial glycemic response to carbohydrates as they are digested. Jenkins et al. proposed quantification of postprandial glycemic response in the form of the glycemic index in 1981.[15] They established a means of measuring glycemic response by comparing a test food that contained carbohydrates with an equal amount of glucose (50 g of the test carbohydrate/50 g of glucose).[16,17] It was found that a 50 g baked white potato provided the same glycemic effect (100%) as an equivalent amount of simple sugar; whereas 50 g of pasta provided 35% of the glycemic effect of 50 g of simple sugar. Thus, the potato scored 100 on the glycemic index and the pasta scored 35. It was hypothesized that foods with a high glycemic index tended to overstimulate β-cell production of insulin. The resulting hyperinsulinemia would contribute to heightened insulin resistance, which combined with hyperglycemia would lead to glucotoxicity and further β-cell dysfunction. If the hyperglycemia worsened, there was a greater risk of increases in free fatty acid levels. Consequently, β-cells would be further exhausted resulting in decreased available insulin. In pregnancy, this cycle would be exaggerated leading to sustained hyperglycemia with relative insulin deficiency.

After several years of testing the glycemic index approach, it was found that the glycemic index was a function of myriad interrelated factors: meal composition, food preparation, and rate of ingestion.[18] This led to disagreement as to whether carbohydrates should be measured solely by their glycemic index. Because most diets include mixed meals with different metabolic rates, arguments were put forth to make all carbohydrates equivalent. However, some investigators still disagree.[19] Moses et al. showed that improved glycemic control and avoidance of insulin therapy were feasible if the patient were assigned a diet with a low glycemic index.[20] Concluding that, "Women randomly assigned to receive a low glycemic index diet were able to lower the glycemic index of their diet rapidly and maintain this lower level for the duration of pregnancy." Furthermore, the low glycemic index diet reduced "the need for the use of insulin without compromise of obstetric or fetal outcomes."[17]

In spite of the controversy, or perhaps because of it, carbohydrate counting which assumes that 15 g of any carbohydrate (a carbohydrate choice) are equivalent in terms of their postprandial effect has become the mainstay of MNT in pregnancy complicated by diabetes. Meals and snacks are apportioned according to the number of carbohydrate choices (without regard to their glycemic index). Since each carbohydrate choice comprises 60 kcal, it is possible to calculate the number of calories from carbohydrates throughout the day and apportion them for each meal and snack. For example, if 40% of the total daily caloric requirements are composed of carbohydrates, and the total daily caloric intake is 2600 kcal, then 1040 kcal would be composed of carbohydrates or approximately 17 choices (1040/60). Assuming 80% of carbohydrates are apportioned to 3 meals and 20% to 3 snacks, then following is the final division of carbohydrate choices: 14 choices for meals and 3 choices for snacks.

Equally controversial is the amount and type of fat consumed by pregnant women with glucose intolerance especially as it is related to weight gain and lipotoxicity.[21] Although it is generally agreed that if total carbohydrates are reduced, fats should be increased proportionately in calories; the amount of saturated, monosaturated, and polyunsaturated fats is unclear. General guidelines range from equal proportions of each type of fat to lower saturated fats and higher polyunsaturated fats.[22] Saturated fats (such as those found in red meat, butter, cheese, and lard) are considered to have the highest association with cardiovascular disease. Monosaturated fats (olive oil) and polyunsaturated fats (vegetable and fish oils) seem to be less associated with cardiovascular disease and in some cases (such as fish oils with omega-3 fatty acids) are anti-inflammatory and antithrombotic.[23]

The role of protein in maternal nutrition has not been clearly established. It has been noted, nevertheless, that too much protein can stimulate excess hepatic glucose output, which will cause an increase in fasting plasma glucose and consequently in free fatty acids.[5] Generally, protein is restricted to no more than 20% of total caloric intake and is distributed equally throughout each meal.[3]

Fiber is often considered the "fourth" constituent of MNT because of its potential for glucose lowering. Foods composed of water-soluble fiber such as fruits act to delay the intestinal absorption of carbohydrates thereby slowing the conversion of carbohydrates to glucose. This lessens their impact on postprandial blood glucose. In contrast, foods high in water insoluble fiber, such as vegetables, appear to have little impact on blood glucose level. Most recommendations for MNT include at least 30 g of fiber with emphasis on at least one form of water-soluble fiber with each meal.[5,6,12,13]

STARTING MEDICAL NUTRITION THERAPY

Since the final distribution of calories is subject to diurnal glucose patterns, weight, and ketones, an approach to MNT that starts from a fixed caloric distribution with adjustments based on these metabolic parameters seems reasonable. One such approach is illustrated in Figure 15–3.[24] For both consistency and simplicity, the following proportions are used: 40% carbohydrates, 20% protein, and 40% fats. The carbohydrates are divided into <25% simple sugars (or low fiber, high glycemic index) and 75% complex carbohydrates (or high fiber, low glycemic index) to lessen the overall postprandial glycemic impact of simple sugars and foods/drinks low in fiber. The source of protein and fats are selected to lessen the long-term risk of macrovascular disease. Foods high in saturated fats are less than 10% of total fat intake. This proportion of carbohydrates, protein, and fat is maintained for both meals and snacks. To avoid carbohydrate loading and subsequent hyperglycemia, no meal is overbalanced with carbohydrates. Meals constitute 85% of the total caloric intake, with snacks comprising the remainder. The division of total meal calories into three primary meals is also subject to controversy. Recommendations of between 10% and 25% for breakfast, with equally wide variations for lunch and dinner, reflect the degree of disagreement and a lack of sufficient studies to guide clinical decision. However, if clinical parameters (glucose level, weight, and ketones) are relied upon, the exact division between meals seems less significant. Notwithstanding the disagreements, a reasonable starting point for total calories is 20% breakfast, 30% lunch, and 35% dinner, with the remainder reserved for snacks. To assure adequate intake of vitamins and minerals, the RDA for pregnancy is followed.[5]

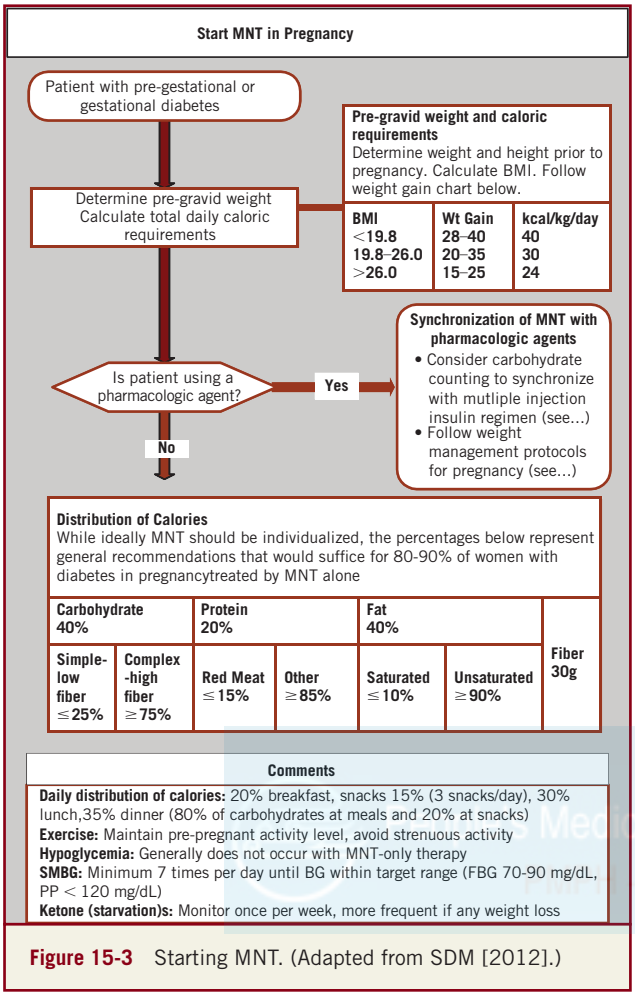


Figure 15-3 Starting MNT. (Adapted from SDM [2012].)

SYNCHRONIZATION OF MNT WITH PHARMACOLOGIC TREATMENT

When pharmacologic agents are necessary to control blood glucose levels, whether for pregestational or gestational diabetes, the challenge is how to integrate MNT without subjecting the patient to a fixed routine. Traditional therapies synchronize food intake with the pharmacokinetics of the drug. This approach generally recommends large meals and small snacks to match the action curves of regular and intermediate-acting insulin (still the most popular insulin-based regimen). Regular insulin (R) requires a meal that assures sufficient mixed carbohydrate content to meet a peak action that begins within 30 minutes after the injection of insulin and lasts up to 90 minutes. Since intermediate-acting insulin (NPH) is generally administered with the regular insulin, a second meal consisting of substantial carbohydrate content is required between five and seven hours after the injection of R/NPH to match the peak action of the intermediate-acting insulin. If the patient is limited to two injections of this mixed insulin regimen, then each day's meals have to be planned with precision and executed without variation.

More contemporary approaches to insulin-based therapies utilize multiple injection regimens relying on rapid-acting insulin to accommodate meals and snacks (bolus) and intermediate- or long-acting insulin for overnight blood glucose control (basal). These regimens attempt to fit the lifestyle and eating habits of the patient by depending on frequent SMBG or CGM readings to guide insulin dose and dietary composition (see Figure 15-4). Patients test their glucose before each injection of insulin, during and after completion of each meal. If the glucose is higher than target, they administer a small amount of rapid-acting insulin, or if it is below target, they have a snack with sufficient carbohydrates to increase glucose levels to within target. Once glucose is stabilized, the patient can estimate the amount of rapid-acting insulin associated with a carbohydrate choice by dividing the total number of units of rapid-acting insulin by the total number of carbohydrate choices. This experiential approach is called intensive insulin management or basal/bolus insulin treatment. It can be used with equal effectiveness in both pregestational diabetes and GDM.

Currently, glyburide (sulfonylurea) is the only noninsulin agent shown to significantly reduce glucose levels and restore euglycemia in a large population of pregnant women with dysglycemia (GDM and type 2).[25–27] Dietary management integrated with glyburide-based therapy has not been widely studied. However, since the pharmacokinetics of glyburide have been well documented, there is no reason to assume any difference in action during pregnancy. Sulfonylurea drugs attach to receptors on the potassium channel of pancreatic β-cells facilitating the release of insulin without regard to prandial state or glucose level. MNT must take into account the necessity of not missing meals and of knowing the glycemic level as the risk of hypoglycemia is increased when glyburide is present in the absence of exogenous nutrition. Consequently, frequent self-monitored blood glucose (SMBG) or continuous glucose monitoring (CGM) is a critical component to assure synchronization of glyburide action with energy intake.

MONITORING

As mentioned earlier, at the onset and throughout treatment for diabetes in pregnancy, three metabolic parameters should be monitored: glucose, weight, and ketones. Although women placed on MNT alone are considered less prone to ketosis or hypoglycemia than women treated with insulin or glyburide, they require the same surveillance. Because of their compromised ability to respond to changes in diurnal glucose patterns, these women are at an especially high risk of both ketosis and hypoglycemia during periods of severe morning sickness accompanied by vomiting. If prolonged ketosis occurs, there is a risk of adverse fetal neurodevelopment.[28] For these women, close monitoring of ketones is essential. In addition, women with significant morning sickness accompanied by vomiting are subject to hypoglycemia due to loss of nutrients. For women treated with a pharmacologic agent, these risks are more pronounced. Both insulin and glyburide are hypoglycemic agents. Periods of undernourishment are especially prone to low blood glucose. Thus, frequent SMBG or CGM is advised. Finally, for women treated by diet alone or in combination with a pharmacologic agent who choose to significantly reduce caloric intake to control glucose levels, both starvation ketosis and hypoglycemia can subsequently occur. Weight loss in pregnancy may be the first indicator of this behavior.

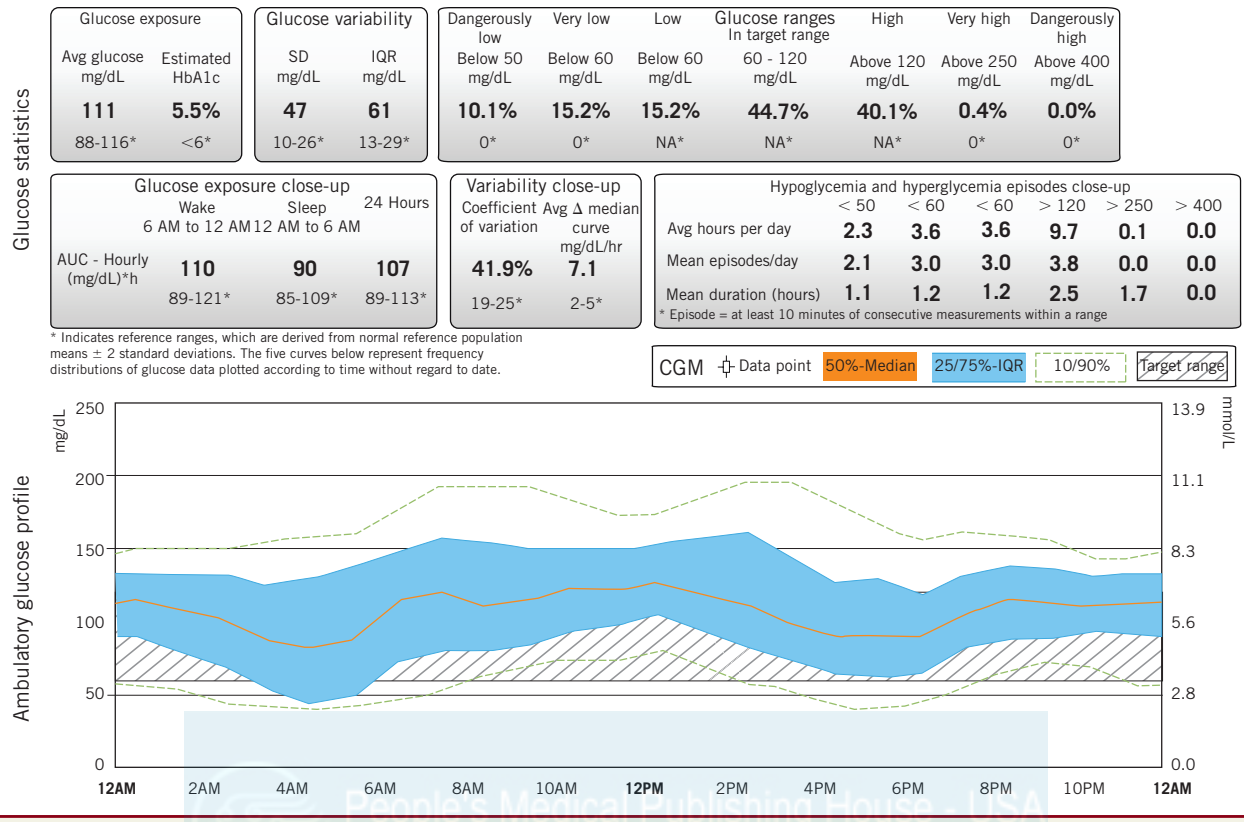


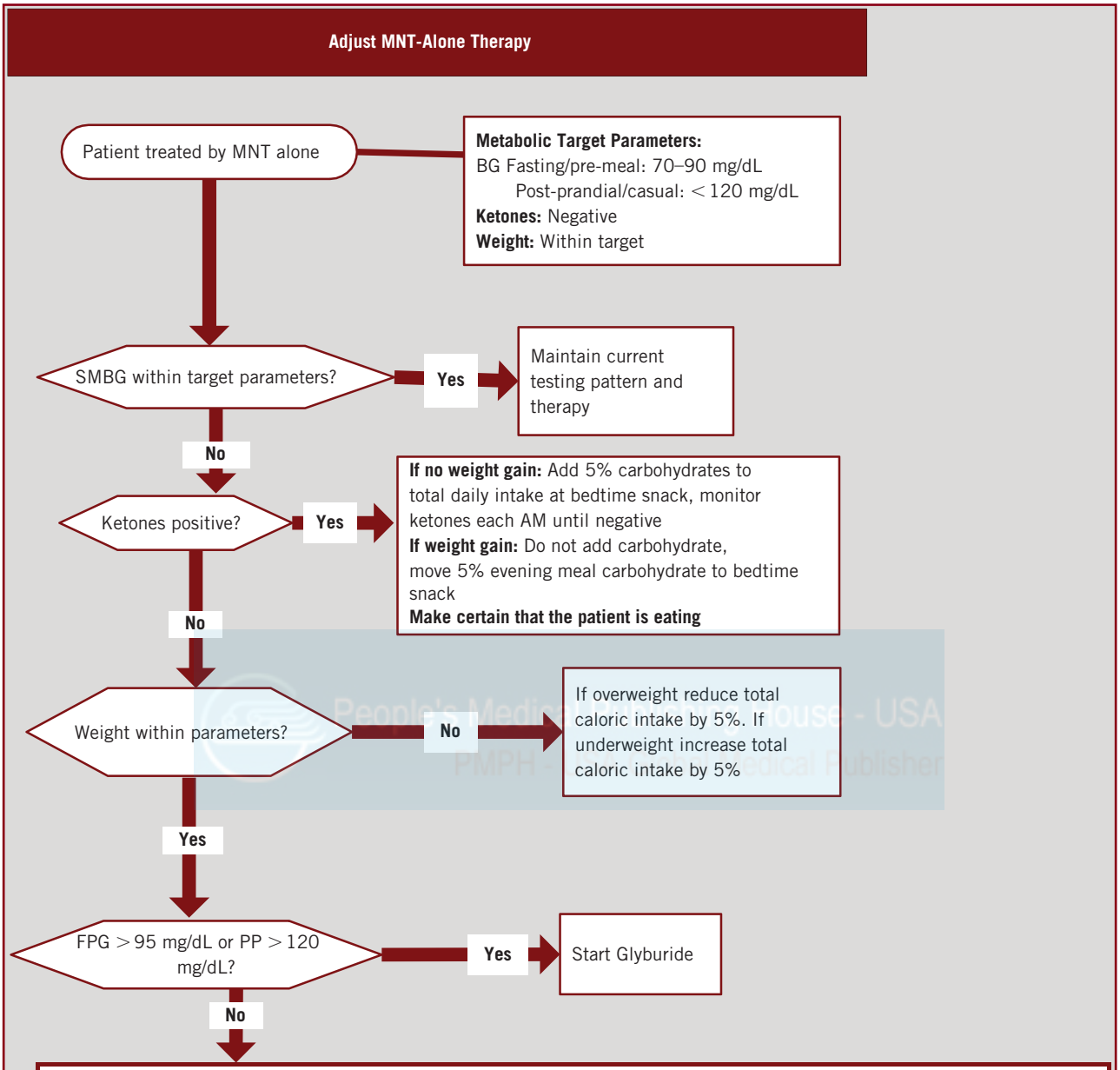
Figure 15-4 AGP of subject with pregestational type 1 diabetes in her 25th gestational week. Note that the target (parallel lines) is set at between 120 and 60 mg/dL. More than 44% of the values remain within target with one period, 9 to 11 AM showing a postprandial hyperglycemic peak. Two periods, 2 to 6 AM and 3 to 7 PM, show between 10% and 25% hypoglycemia. Although the latter may be indicative of too much rapid-acting insulin before the meal, note also that the evening hypoglycemia is balanced by an equal risk of hyperglycemia; consequently, changes in the meal are indicated. The early morning hypoglycemia may be due to overnight basal insulin, thus reducing the evening dose would be in order.

Taking all these issues into account, the most ideal and physiologic approach to monitoring would be the employment of CGM since it provides diurnal glucose patterns that are generally not achievable with SMBG. However, owing to the high cost and poor reimbursement for this new technology, SMBG can be used in a more physiologic manner. Random testing at least seven times each day plus once each overnight period for at least one week will provide a generalized view of the patients' diurnal glucose patterns. The testing is random so that it accounts for all time periods rather than limited to before and after each meal and at bedtime. This does not replace the necessity for patients treated with insulin or glyburide to test immediately before administration of either pharmacologic agent. This assures that the there is a lower risk of hypoglycemia. An easy schedule for random testing is fasting, between one and four hours after each meal, and at bedtime. For overnight at between 1 and 4 am, each night should be sufficient.

ADJUSTMENTS IN MNT

Dietary adjustments for women treated by MNT alone (see Figure 15-5) begin with an assessment of current diurnal glucose patterns, weight, and ketones. If these variables are within target parameters, further changes in therapy are unnecessary. If ketones are positive and fasting glucose is below target, the most likely cause is undernourishment. If ketones are positive and all glucose values are below target, the undernourishment may lead to sustained hypoglycemia. In both cases, additional carbohydrates before bedtime and throughout the day are advised. The ratio of carbohydrates at meals and snacks can be adjusted with more carbohydrates provided by snacks to increase blood glucose between meals. If ketones are negative and weight gain is outside of target parameters, reduction in total caloric intake of 5% will not risk undernourishment and may slow weight gain. If there is weight loss with negative ketones, an increase in total calories by 5% should re-establish appropriate maternal/fetal nourishment.

Blood glucose parameters are perhaps more critical than any other metabolic indicator for women treated by MNT alone. Unlike pharmacologic interventions, there is the assumption that reliance on nutritional therapies only indicates that the disorder is "inconsequential." From a behavioral perspective, it is likely that the patient may not consider GDM or type 2 diabetes as serious diseases because they are only being treated by dietary changes;



Dietary Adjustment
Redistribute total daily caloric intake (see guidelines below) based on weather FPG or PPBG or both are below target.

BG	Fat	Carbohydrate	
Fasting < 70	35%	45%	70% meals
			30% snack
PP < 90	30%	50%	80% meals
			20% snack
Fasting < 70 & PP < 90	25%	55%	75% meals
			25% snack

Figure 15-5 Adjusting MN.

however, epidemiological data suggest otherwise. If glucose is not well controlled, the risk of adverse perinatal outcome may be as high or higher in women treated by MNT alone for GDM or type 2 diabetes as in women treated by pharmacologic intervention.[29] If fasting glucose is >95 mg/dL or postprandial is consistently >120 mg/dL, the risk of adverse perinatal outcome increases by as much as 14-fold.[30,31] There are insufficient data to suggest that MNT alone is effective when glucose is elevated to these levels. Consequently, pharmacological interventions, either glyburide or insulin, are appropriate for women with GDM or type 2 diabetes.

Effective utilization of dietary changes to improve glycemic control requires addressing the carbohydrate and fat content of meals and snacks (see Figure 15-5). When fasting glucose is <70 mg/dL for three consecutive days, then an increase in the amount of complex carbohydrates (low glycemic index) at bedtime is indicated. Complex carbohydrates containing water-soluble fiber are preferable. Since additional calories are not required, calories from fat should be reduced by an equivalent amount. When postprandial glucose is persistently below target for three consecutive days, the proportion of fat is decreased by up to 10% and carbohydrates (low glycemic index preferred) increased by up to 10%. Since total caloric intake is unchanged, weight should remain within target parameters. When fasting and postprandial glucose are below target and ketones are negative, diet can be adjusted to *as low as* 25% fat and *up to* 55% carbohydrates. In this instance, carbohydrates are divided into 75% meals and 25% snacks. This assures that the glycemic response of increased carbohydrates is evenly distributed without risk of hyperglycemia. Continued close surveillance of weight, glucose, and ketones assure the optimization of this approach to MNT alone. When MNT is used in combination with a pharmacologic agent to achieve glycemic targets, the challenge is to optimize both therapies (see Figure 15-6).[18]

Approaching modifications in MNT from an experiential base allows rapid adjustments that take into account the action of both the pharmacologic agent and the dietary nutrients. Assuring that the metabolic parameters are intact is essential. If ketones are positive and starvation ketosis is suspected, reduction in the evening or bedtime dose of the pharmacologic agent is suggested along with the redistribution (not addition) of carbohydrates at bedtime. If the patient is experiencing excessive weight gain, reduction in total caloric intake by 5% should be instituted first. If the total reduction in calories is composed of fats, it is unlikely that a change in medication dose is required. However, if carbohydrates are reduced, then close monitoring of glucose with appropriate adjustments in medications are recommended.

BEHAVIOR MODIFICATION, PATIENT SELF-CARE EDUCATION

Behavioral approaches begin by setting individualized dietary goals following a period of education designed to link energy intake with weight management and blood glucose control. Prochaska et al. argue that behavior modification in chronic disease requires an assessment of the patient's willingness and readiness to change.[32] Essentially, they maintain that patients will not change eating behaviors unless they understand the rationale for the change and are ready to set short-term goals. Consequently, individuals with maternal diabetes need to learn about their disorder from several perspectives: etiology, treatment, complications, fetal development, delivery, postpartum follow-up, and self-care skills. These subjects constitute a substantial amount of learning that must take place within a relatively brief period of time if patients are to participate in their care. Most education/skills programs focus on the development of self-care "survival" skills first. For all women, independent of treatment, self-monitoring of blood glucose, and measurement of ketones are essential elements of self-care. For women treated with insulin for the first time, injection technique and insulin administration are emphasized. Recently, some educational programs have included a trial injection of saline for all women to remove any barriers (such as needle phobia) to eventual insulin administration. Nutrition and its relationship to glucose control is generally an early topic. Meal and snack planning skills, including carbohydrate counting, nutrient requirements, and healthy food choices, are part of the self-management skills set. If nutritional counseling is available, an individualized food and activity plan that is culturally and economically sensitive is developed.

The nutritional tools that the patient is taught vary. Fixed caloric intake with preset meals and snacks, an exchange list with "allowable foods and drinks" and carbohydrate counting are three of myriad dietary interventions. There is insufficient evidence to suggest that one is more successful at achieving dietary goals than the other. However, there is an emerging fourth approach that combines some of the elements of all these approaches. Based on both behavior modification and clinical metabolic parameters, the approach, "Replace, Reduce, Restrict," provides a stepwise tactic that allows the patient to "experiment" with different dietary strategies.[24] After a mutually acceptable set of short-term dietary goals are set, the patient begins by replacing foods and drinks high in carbohydrates with the same quantity of food or drink but with lower carbohydrate content. For example, an 8 oz. regular soft drink is replaced by an 8 oz. diet soft drink or a medium potato is replaced by 1/2 cup pasta. This replacement is made initially at one meal or snack and then increased to a goal of replacing high carbohydrate foods and drinks at every meal and snack. If this fails to achieve clinical goals, then reducing total caloric intake is attempted. In this strategy, the patient is asked to reduce each portion size. By maintaining only one change in behavior, the patient can focus on this behavior. Generally the portions sizes are decreased by increments of 5%. To reinforce the changes, the patient is asked to use the same plate, bowl, and drinking glass. In this manner, changes in the quantity of food can be observed. If this fails to achieve metabolic targets, then restrictions of specific foods and drinks are employed. The stepwise procedure can be combined, and the patient eventually may choose to replace some foods, reduce the intake of specific drinks, and accept restrictions of certain snacks. These dietary changes require ample time to be initiated and substantial time to be reinforced.

When adjustments to medications occur, dietary change (principally in carbohydrates) can assist in achieving glycemic control and should also be considered. When glucose is below target, the first step is to lower the medication that is most closely associated with the period of persistent hypoglycemia. If this fails to improve control to reach target, the

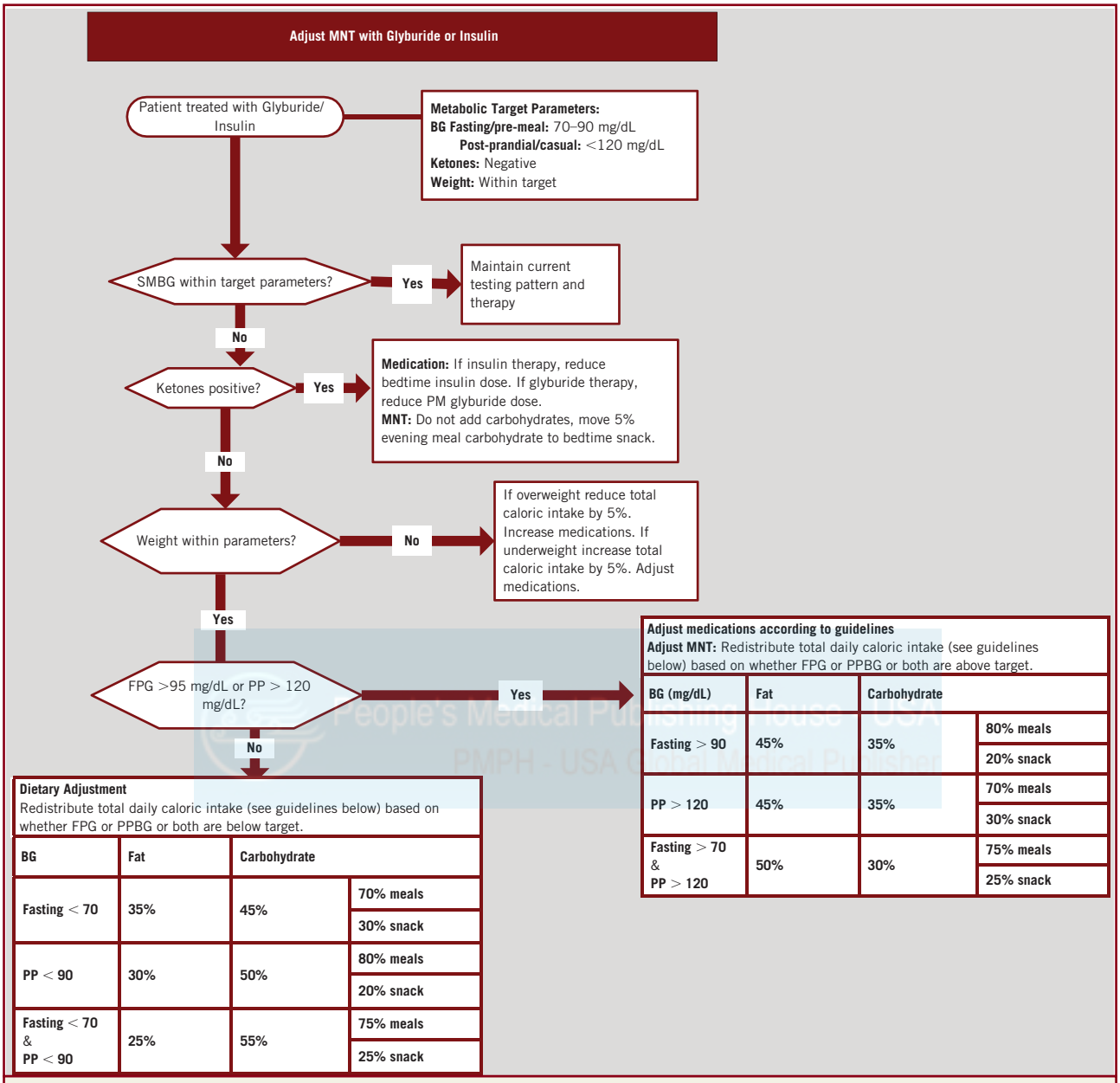


Figure 15-6 MNT in combination with glyburide or insulin.

composition of carbohydrates in the daily caloric intake is increased between 45% and 50% and fats can be reduced proportionately. The distribution of carbohydrates between meals and snacks is recalculated to correspond with changes in medication dose. If glucose is above target, medication is increased combined with a decrease (to no less than 35%) in proportion to carbohydrates. The distribution between meals and snacks is different dependent on the pattern of hyperglycemia. Fasting hyperglycemia suggests maintaining a ratio of 80% carbohydrates at meals and 20% at snacks, whereas persistent hyperglycemia throughout the day suggests a ratio of 75% meals to 25% snacks, thereby spreading the glycemic response throughout the day.

DIETARY CONTROVERSIES: ARTIFICIAL SWEETENERS, FAD DIETS, DRUG INTERVENTIONS

The US Food and Drug Administration lists four approved artificial sweeteners: saccharin, aspartame, acesulfame potassium, and sucralose.[33] The American Diabetes Association, in its 2012 position statement regarding nutrition, appears to concur that these artificial sweeteners are safe in pregnancy.[12] There are no significant studies regarding the safety or efficacy of artificial sweeteners in maternal diabetes. Both saccharin and aspartame have been subject to claims of linkage to cancer, brain tumors, and other medical conditions. However, repeated studies have not confirmed

the association, thus both remain approved. Acesulfame potassium and sucralose are generally used in processed foods and have also been subjected to continual testing. No associations between these sweeteners and disorders of pregnancy have been uncovered.

Fad diets fall into five general categories: (1) starvation (<200 kcal/d); (2) very low calorie (approximately 800 kcal/d); (3) low energy (800–1600 kcal/d); (4) low fat (<20% of calories); and (5) low carbohydrate (<25 g/d).[34] None of these diets have been tested in maternal diabetes nor do they appear to provide any reasonable scientific basis for use in pregnancy. Reliance on these diets could have serious detrimental effects for fetal growth and development and for maternal glycemic control. There are also pharmacologic agents that are currently used in diabetes that have been shown to improve weight management and aid weight loss. They are acarbose, metformin, orlistat, and sibutramine. Acarbose, an alpha-glucosidase inhibitor, has been used in the treatment of type 2 diabetes to slow the absorption of carbohydrates, thereby reducing the postprandial glucose response. Metformin, a biguanide, has been extensively used in the treatment of both type 2 diabetes and polycystic ovary syndrome (PCOS). Its weight management effect is twofold, and it suppresses excess hepatic glucose output, and due to gastrointestinal distress, it appears to lessen appetite. It has been used in pregnancy generally during the first trimester in patients with PCOS. Orlistat, a lipase inhibitor, also appears to have two effects on weight maintenance and weight loss. Its principal action is to block or slow the absorption of fat; its secondary action is to produce uncomfortable gastrointestinal side effects in patients who persist in consumption of foods high in fat. Sibutramine is a new class of drugs that acts on the central nervous systems to suppress appetite. It is reported to provide the patient with a sense of "fullness." Generally, since all these pharmacologic agents pass the placental barrier and their effect on the developing fetus is unknown, they are not recommended for use in pregnancy. The exception may be metformin which although it passes through the placental barrier, it has beneficial effects during the first trimester that may balance any risks.

The use of MNT alone or in combination is a matter of balancing the energy intake with output which assuring normal fetal growth and development. Preconception counseling and glycemic control are the primary principals of reducing the risk of adverse perinatal outcomes. These principals are especially important in women with pre-existing diabetes or at high risk (obesity, family history of type 2 diabetes, previous GDM, or previous large for gestational age (LGA) or macrosomia) for glucose intolerance in pregnancy. Initiation of tight glycaemic control by diet alone or in combination with pharmacologic agents must be started prior to conception to assure a health physiological milieu for the mother and fetus.

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The Use of Insulin in Diabetes in Pregnancy

16

From the Old to the New

Oded Langer, MD, PhD

Doctors pour drugs of which they know little,
To cure diseases of which they know less,
Into patients of whom they know nothing.

—Voltaire

Key Points

- Insulin therapy should mimic as much as possible the physiological pattern of insulin secretion.
- There are different patterns of insulin requirements for gestational diabetes mellitus (GDM; bi-phasic) and pre-existing diabetes (tri-phasic).
- Regular human insulin, despite improved purity and stability, does not successfully imitate physiological insulin secretion.
- Regular human insulin should be administered 30 to 45 minutes prior to eating; its peak effect occurs 2 to 4 hours after the injection and its duration of action lasts 6 to 8 hours.
- Short-acting insulin analogs successfully imitate physiological insulin secretion. They are absorbed quickly, achieving peak plasma concentrations about twice as high and within approximately half the time compared to structurally unchanged insulin.
- In GDM women, fasting plasma glucose of ≥95 mg/dL is the threshold for insulin initiation; insulin dose is unlimited.
- Self-monitoring blood glucose is a prerequisite for insulin therapy.

INTRODUCTION

In 1889, von Mehring and Minkowski identified the pancreas as the origin of diabetes mellitus. Thirty-two years later, Banting, Best, Collip, and Macleod successfully extracted and introduced the active factor, insulin, and soon followed with its administration to a young patient in Canada. The stage was set for a new era of diabetes care and research with the ultimate goal of disease prevention and/or discovery of a cure. Since the breakthrough of the source of this complex metabolic disorder, there have been major developments in insulin production, refinement, pharmaceutical formulation, and methods of delivery. However, the persistent complications that lead to morbidity and mortality in patients with GDM and type 1 and type 2 diabetes are an unrelenting reminder that we may have won many of the major therapeutic and management battles but are still far from winning the war.[1–3]

There are approximately 120 to 150 million people worldwide who suffer from diabetes. According to the World Health Organization (WHO), in some parts of Africa, the mortality rate from insulin-dependent diabetes is estimated at 50% in the first five years of the illness. In many African countries, insulin-dependent diabetes is a death sentence, since the insulin may be unavailable or beyond the purchasing power of the patient's family. In Russia, access to insulin is restricted. Under Communism, the Russian medical services supplied medicine including insulin to people who needed it. When Communism collapsed and free enterprise moved in, the situation in Russia changed, that is, only people with money could afford insulin. According to a 1997 International Diabetes Federation Task Force survey, "15 countries (out of 73 countries surveyed) have severe problems with access to insulin," www.diabetesinterview.com (April 2000). The main barriers to insulin access appear to be affordability, distribution, and transportation. Another major barrier includes the luxury tax laws and war. Although the WHO has listed insulin as an "essential drug," and, therefore, should not be taxed as a luxury item, several countries still tax insulin, for example, the Philippines. Obtaining insulin and proper diabetes care in a poor country is a major challenge for diabetic sufferers. However, most authoritative bodies and researchers neglect to address the drain that this disease causes on family resources, www.diabetesinterview.com (April 2000).

THE PHYSIOLOGY OF INSULIN

Insulin is produced in the beta cells of the islets of Langerhans as a single polypeptide precursor, preproinsulin, which is then converted to proinsulin and 86-amino acid polypeptide. Proinsulin forms equimolar amounts of insulin and C peptide (i.e., connecting peptide) through the removal of 4-amino acid residues. The resulting insulin consists of a 20-amino acid A chain and a 31-amino acid B chain connected by two disulfide bridges, with the addition of a third disulfide bridge within the A chain. The final product that is released from the beta cells into the portal venous system is 90% to 97% insulin with an equimolar amount of C peptide. Proinsulin and the intermediates of change comprise the remainder.[4]

The liver removes about 50% of the insulin that is released into the portal system during its first passage.[5] However, since the amount the liver extracts is variable, estimating the rates of insulin secretion based on peripheral venous concentrations is inexact. C-peptide is primarily cleared by the kidney, and this has, under various conditions, provided the precise quantification of insulin secretion rates. Insulin secretion into the portal system occurs in the basal state at a rate of about 1 U/h in normal adults. A 5- to 10-fold increased rate of insulin secretion occurs with the intake of food. The total daily secretion of insulin is approximately 40 U.[5]

Insulin secretion rates in either the fasting or the postprandial state decrease rapidly to prevent hypoglycemia with moderate exercise. With strenuous exercise, hyperglycemia may occur and result in enhanced secretion of insulin in the postexercise period. Therefore, insulin's secretory responses to physiologic stimuli are multifaceted and present a challenge to care providers and researchers trying to duplicate them with available therapeutic regimens.[6–8]

In general, exercise helps diabetic patients improve their ability to metabolize glucose. But for those people who are not inclined to use exercise machines such as the treadmill or Stairmaster, the exercise involved in walking downhill leads to even bigger improvements than hiking up! A study conducted in Austria found that both forms of exercise improved glucose tolerance but that the downhill hike had a greater effect—a 25% change in tolerance compared with 9% after the stint of uphill climbing. This finding may be explained by the fact that eccentric exercise (muscle cells are lengthened as they resist a force) may increase blood flow more than concentric (muscle cells shorten to exert force on an object) exercise.[9]

A Finnish study found that physical activity on the job was as effective as leisure-time workouts in reducing deaths from heart disease among patients with type 2 diabetes. When the survey data were adjusted to account for factors such as age and weight, researchers found that having an active job or participating for more than three hours a week of a demanding leisure-time activity cut the risk of death from heart disease by approximately 33%. However, since more and more jobs are sedentary, the researchers recommended exercising during work breaks, walking more on the job, or walking to work.[10]

INSULIN ANALOGS

The development of drugs is driven by the goal to correct pathophysiology to approximate normal physiology. Normal secretion of insulin includes a basal stage that prevents excessive hepatic production and mobilization of free fatty acids from the adipose tissue stores. This basal insulin is needed regardless of meal pattern and patient physical activity. The second component in insulin physiology is related to insulin secretion in association with meals. Ninety percent of nutrients are absorbed within 90 minutes after a meal. After two hours, the plasma glucose and insulin levels return to normal premeal values.[11]

Several generations of insulin have been developed since its original discovery. Today the most commonly used are human and insulin analogs. Regular human insulin, despite improved purity and stability, is not entirely successful in imitating physiological insulin secretion. It should be administered 30 to 45 minutes prior to ingestion of a meal; its peak effect occurs two to four hours after the injection, and its duration of action lasts for six to eight hours. The pharmacokinetics following subcutaneous injection of regular or soluble human insulin preparations makes it difficult to achieve day-long normoglycemia. This low rise to peak insulin concentration is likely to account for much of the observed hyperglycemia following meals in people with diabetes. The delay in the absorption of subcutaneously administered structurally unchanged insulin is due to the fact that in this preparation, insulin tends to associate in "clusters" of six molecules (hexamers), and time is needed after injection for these clusters to dissociate to single molecules that can be used by the body.[12] There is often nonadherence to the insulin protocol due to the inconvenience and limitations of injecting approximately a half hour prior to a meal so the patient ultimately takes the insulin with the meal (Table 16-1).[13]

Considerable research in the past two decades has been devoted to the development and improvement of insulin analogs with pharmacokinetic profiles that differ from those of existing insulin preparations. Insulin lispro is an analog of human insulin (HumalogP) in which the amino acids praline and lysine, which occupy B28 and B29 positions, respectively, are interchanged. Although insulin lispro, like soluble insulin, forms hexamers, they dissociate more rapidly following subcutaneous injection.[14]

In the short-acting insulin analog aspart (NovoRapidR), praline at position 29 of the B-region is replaced by aspartic acid. The change reduces the stability of the interactions within the hexamer, thereby increasing absorption of the insulin after injection.[15] Aspart can be administered shortly before a meal but with the addition of basal insulin to preclude late postprandial and fasting hyperglycemia. Studies of aspart involving nonpregnant type 1 diabetic patients reported decreased postprandial glucose concentrations, a reduction in nighttime hypoglycemia, and overall improvement in glycemic control and enhanced patient satisfaction. In addition, hemoglobin A1C values were lower with comparable frequency of adverse events as with the use of regular insulin.[16,17]

Short-acting insulin analogs are, therefore, absorbed more quickly, achieving peak plasma concentrations about twice as high and within approximately half the time compared to structurally unchanged insulin.[18,19] These analogs facilitate lower glucose levels after meals[18,20] and should enhance overall glycemic control. Haffner proposed that lowering postprandial glucose levels may be associated with a decreased risk for developing cardiovascular complications in diabetes.[21] One suggested advantage of short-acting insulin analogs is the possibility to inject insulin immediately before meals, even if in daily life, most diabetic

TABLE 16-1 Action Profile of Commonly Used Insulins

Type	Onset of Action	Peak of Action (h)	Duration of Action (h)	FDA Pregnancy Classification	Cross Placenta	Excreted in Breast Milk
Insulin Lispro	1–15 min	1–2	4–5	B	Minimal	No
Insulin aspart	1–15 min	1–2	4–5	B	Minimal	No
Regular insulin	30–60 min	2–4	6–8	B	Yes	Yes
Isophane insulin Suspension	1–3 h	5–7	13–18	B	Unknown	No
Insulin zinc Suspension	1–3 h	4–8	13–20	B	Unknown	No
Extended insulin Zinc suspension	2–4 h	8–14	18–30	B	Unknown	No
Insulin glargine	1 h	No peak	24	C	Minimal	Unknown
Insulin detamir	1 h	No peak	14	C	Unknown	Unknown

patients seem to use short- or even no injection-meal interval.[20] Further proposed advantages in terms of quality of life are changes in injection modes with the possibility of injecting short-acting insulin analogs after meals.[22]

Treatment with the two short-acting insulin analogs (Lispro—HumalogR; Aspart-Novo RapidR) currently available on the market is promoted with purported advantages with respect to metabolic control and reduced incidence of hypoglycemic episodes for patients with type 1 or type 2 diabetes, diabetic children, and diabetic pregnant women.[23–25] On the other hand, another study failed to show a positive effect on overall blood glucose levels when short-acting insulin analogs were compared with structurally unchanged insulin.[26] In the case of hypoglycemic episodes, two other studies reported contradictory results with respect to hypoglycemic episodes.[27,28] Insulin treatment strategies where short-acting insulin analogs can be used include intensified insulin therapy (short-acting insulin before meals, basal insulin at bedtime or twice daily, including adjustment of insulin dose based on carbohydrate intake) or conventional insulin therapy (basal or premixed insulin up to three times daily with or without oral hypoglycemic agents). Only patients treated with continuous subcutaneous insulin infusion (CSII) performing intensified insulin therapy showed a significant decrease in HbA1C when short-acting insulin analogs were used in the nonpregnant state.[29,30] Insulin analogs are more expensive than structurally unchanged insulin, and in the year 2000, insulin lispro and insulin aspart had a 30% share of the market for short-acting insulin in most developed countries.

Insulin lispro is 1.6-fold more potent than human insulin in binding to human placental insulin-like growth factor I (IGF-I) receptors. Both have 0.2% of the binding capacity of IGF-I itself.[31] Structural homology of insulin analogs to IGF-I has caused concern regarding the progression of late complications and potential mitogenic (induction of cell division) effects, especially with long-term use of insulin analogs. IGF-I may affect the progression of retinopathy,[32,33] and certain modified insulin analogs have shown a carcinogenic effect in the mammary glands in female rats[34] or mitogenic potency in osteosarcoma cells.[31] Despite the potentially adverse properties of insulin analogs, very limited data on long-term safety are currently available, mainly because patients with clinically relevant microvascular complications have been excluded from most clinical trials. In summary, to prevent adverse outcomes such as congenital malformations and macrosomia, it is recommended that patients be placed on a regimen of daily multiple injections of rapid- and long-acting insulin, or an external insulin pump, together with intensive blood glucose self-monitoring. Rapid-acting insulin analogs such as lispro and aspart are now widely used during pregnancy in women with type 1 diabetes with demonstrated efficacy and safety.[35,36]

INTERMEDIATE- AND LONG-ACTING INSULIN

Evaluation of the teratogenicity of a medicinal product in humans requires a sample size large enough to show an increase in the occurrence of rare events. If the risk of malformation in a given population is only 3%, then at least 220 to 240 pregnancies need to be analyzed to detect a two- to threefold increase with a power of 80%.[37] The use of long-acting insulin analogs (glargine and levemir) is currently not recommended during pregnancy. However, since treatment with glargine can facilitate good glycemic control with a reduced risk of hypoglycemia, it may be a valuable alternative in the management of pregnant women with type 1 diabetes. Moreover, since many patients with type 1 diabetes are usually already being treated with short- and long-acting insulin analogs, they may be reluctant to change their insulin regimen when planning a pregnancy if their diabetes is already well controlled.

Intermediate- and long-acting insulin are components of the insulin algorithm in the care of patients. The neutral protamine hagedorn insulin (NPH) is more commonly used than the lente and the ultra-lente insulin in pregnancy mainly because its absorption pattern and duration are more accurate. However, the 24-hour NPH concentration pattern is not ideal and resembles a bimodal distribution; therefore, it cannot create a stable monotonous basal level throughout the day (Figures 16-1 and 16-2).

Insulin glargine and detemir are long-acting insulin analogs that were developed to mirror the basal pancreatic insulin secretion. However, neither has been tested in pregnancy for

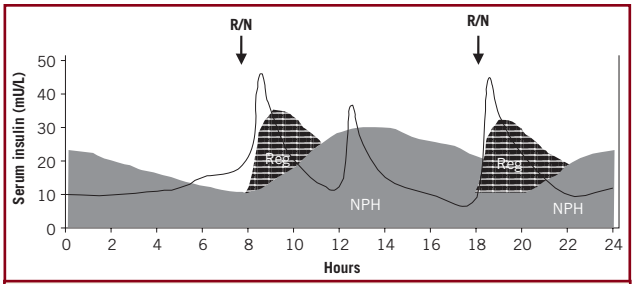

Figure 16-1 Insulin action: regular/NPH.

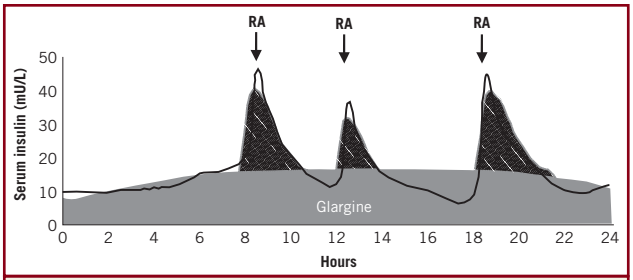

Figure 16-2 Fitting insulin. Lispro or aspart with insulin glargine.

placental transfer and effect on the fetus; they are not currently recommended in pregnancy. Glargine has high IGF qualities. It has been reported to have 6.5 times more potency than human insulin in binding the IGF receptors.[31] In a malignant cell line, increased mitogenicity was found with glargine versus regular insulin. Finally, a case report suggested that prolonged use of the drug (more than a year) may be associated with progression in retinopathy.[38] Insulin glargine is an analog in which glycine is substituted for aspartic acid at position 21 on the alpha chain and two basic argenines are added to the C-terminus of the beta chain. The addition of zinc to the molecule results in stabilization of the hexamer (prolongation of molecule action), a decrease in absorption, and increase in association rates. In contrast to NPH, the glargine has a stable monotonous basal profile that minimizes the peaks and valleys in the former insulin. Thus, it has been suggested that the use of glargine results in decreased hypoglycemic episodes when used as part of the insulin administration algorithm in conjunction with lispro or aspart insulin. In the nonpregnant state, the use of glargine demonstrated a decrease in fasting glucose levels, hemoglobin A1C, and nocturnal hypoglycemia.[39,40] Use of glargine in pregnancy may be promising since it has the potential to decrease nocturnal hypoglycemic episodes common with tight glycemic control in type 1 pregnant diabetics. Further studies are needed to test the safety for mother and fetus before recommending its use in pregnancy. This is especially significant since the alteration of the insulin molecule for the creation of the insulin analog results, at least in the case of lispro, in placental transfer that is dose dependent.[38,41]

Reports on animal studies have demonstrated the safety of insulin glargine during pregnancy.[42–45] Studies[46] have reported the perinatal outcomes in 102women with type 1 diabetes treated with insulin glargine before conception and throughout pregnancy. The observed rate of large-for-gestational-age (LGA) infants (30%) compares favorably with the rate of macrosomia seen in infants of women treated with human insulin and is in accordance with a recent pilot study showing that the use of insulin glargine is not associated with an increased risk of fetal macrosomia. However, the current study has certain important limitations that need to be taken into account when interpreting the results. It has the inherent weaknesses of all observational studies, that is, recall bias and the absence of matching. There is also a potential for selection bias, as it involved self-selected rather than population-based centers. Furthermore, data on maternal age, body mass index, duration of diabetes, socioeconomic status, and occurrence of severe hypoglycemia were not included in the data collection process.[47] Some concerns, however, have been raised over the use of glargine during pregnancy since the analog exhibits an increased affinity for the IGF-1 receptor, a tendency that is not seen with human insulin.[48]

Insulin detemir is modified by the addition of 14-carbon fatty acid side chain at position 29 of the beta chain that enhances aggregation and delays absorption.[49] The action profile of detemir is close to the physiological profile of insulin regarding its baseline characteristics. The drug does neither peak like NPH nor is it flat like glargine. In addition, it has been demonstrated that there is a fivefold decrease in potency in binding the IGF receptor in comparison to regular insulin. Many consider it unwise to administer glargine or detemir in the management of diabetes in pregnancy.[31,49] In a randomized study,[50] the authors sought to compare the efficacy and safety of insulin detemir (IDet: $n = 139$) with neutral protamine Hagedorn (NPH: $n = 145$), both with insulin aspart, in pregnant women with type 1 diabetes. They concluded that IDet is as well tolerated as NPH as regards perinatal outcomes in pregnant women with type 1diabetes and no safety issues were identified. But the study also reported 20 cases of early fetal losses and three perinatal deaths. Sixteen children had malformations (IDet: $n = 8/142$, 5.6%; NPH: $n = 8/145$, 5.5%).

In the nonpregnant state, short- and long-acting insulin analogs have been shown to result in better glycemic control with less hypoglycemia than human insulin in subjects with diabetes. Recently, a randomized trial showed similar benefits with short-acting analogs in pregnancy complicated by type 1 diabetes.[36] In contrast, few studies have examined the efficacy and safety of long-acting analogs in women with type 1 diabetes during pregnancy, despite their increasing use in this subject group. Consequently, basal insulin analogs have been used off-label.[51,52]

Insulin detemir is an insulin analog that has a consistent pharmacokinetic/pharmacodynamic profile with lower intrasubject variability in terms of glucose-lowering effect compared with either NPH or insulin glargine in subjects with type 1 or type 2 diabetes. Studies have shown that IDet provides similar glycemic control, but with lower rates of hypoglycemia and less weight gain than NPH insulin in nonpregnant subjects with type 1 or type 2 diabetes. The aim of the study was to compare the efficacy and safety of IDet with NPH in pregnant women with type 1 diabetes. The report presented primary data on perinatal and obstetric pregnancy outcomes. Data on glycemic control, maternal hypoglycemia, and maternal safety were reported separately.[53] The drug has been shown in previous studies to have a consistent glucose-lowering effect and one that was similar in magnitude to that seen with NPH insulin in nonpregnant subjects with type 1 or type 2 diabetes.[54]

In a recent study,[55] the objective was to compare glycemic control and pregnancy outcome in women with type 1 diabetes treated with long-acting insulin analogs detemir or glargine. One offspring in each group was born with a major congenital malformation. However, in the majority of women on detemir, this treatment was initiated after the organogenesis, whereas only a small group was on detemir before conception. The authors concluded that pregnancy outcomes were comparable in women using insulin detemir or glargine. The incidence of severe hypoglycemia was comparable 23% versus 23% (P = .98). Preeclampsia 14% versus 18%, P = .52; lower prevalence of LGA infants in women on glargine 49% versus 30% (P = .046); hemoglobin A1C was comparable at eight weeks (median 6.6% [range 5.6–9.8] vs. 6.8% [5.4–10.1] and at 33 weeks gestation (6.1% [5.1–7.6] vs. 6.2% [4.8–7.2]). Of note, there was slight improvement in small changes (8%) in the level of glycemic control; however, the threshold used was higher than the recommended threshold for prevention of fetal macrosomia (<100 mg/dL, HbA1c 5.5%). The overall results of current studies appear reassuring for the continued use of insulin analogs.[56,57] Another concern has been the increased affinity of insulin glargine for the IGF-1 receptor and, therefore, potential for increasing the risk of excessive fetal growth; this is in contrast to insulin detemir. Surprisingly, results showed a decreased risk of LGA infants in the glargine group compared with the detemir group. The prevalence of LGA infants in the detemir group of 49% is comparable with that generally reported for infants of mothers using human intermediate NPH insulin during pregnancy.[58–60] The prospective randomized study comparing insulin detemir to human intermediate NPH insulin demonstrated no significant differences in the prevalence of LGA infants between the insulin detemir and the human intermediate NPH insulin groups. The incidence of LGA infants reported in the majority of former studies on the use of insulin glargine during pregnancy ranged from 30% to 47%. A single study of 37 pregestational diabetics treated with insulin glargine during pregnancy reported a decreased risk of LGA infants compared with women treated with human intermediate NPH insulin (19% vs. 50%).[43,45,47,61,62]

PREGNANCY AND THE USE OF INSULIN ANALOGS

In pregnancy, data on insulin lispro are limited and abstracted from studies with relatively small sample sizes. Most of these reports demonstrated an improvement in glycemic control and enhanced quality of patient lifestyle. Human insulin became widely available in the 1980s when the preferred method of production was recombinant DNA technology. This led to the availability of mutant insulin (insulin analogs) during the mid-1990s that were designed primarily to have improved pharmacokinetic features for subcutaneous administration.[63] Human insulin is recommended when insulin is prescribed in pregnancy since the use of insulin analogs has not been adequately tested in GDM.[64]

The comparison between lispro and human insulin needs to address not only placental transfer but also the efficacy of one drug over the other as well as the cost/benefit ratio. There is little or no difference between insulin lispro, insulin aspart, and human insulin in receptor binding and metabolic and mitogenic potency with a slightly increased binding of insulin lispro to the receptor for IGF-1.[31] Mounting evidence of the beneficial effects of insulin lispro in type 1 and type 2 nonpregnant diabetic subjects includes decreased frequency of severe hypoglycemic episodes, limited postprandial glucose excursions, and a possible decrease in glycosylated hemoglobin when the drug is administered by continuous subcutaneous infusion.[31] In addition, insulin lispro provides greater convenience in the timing of administration (analogs administered up to 15 minutes after start of a meal compared to soluble insulin taken 30 minutes before the meal), patient satisfaction, and reduction in hypoglycemic episodes. The omission of maternal/fetal outcome data in the majority of these studies limits the ability to draw any firm conclusions about the efficacy of insulin lispro in comparison to human insulin.

Controversy persists on the association of proliferative retinopathy with the insulin lispro. In a cohort of 10 women, with type 1 or type 2 diabetes who had been retinopathy free prior to pregnancy, 3 women developed proliferative retinopathy that required laser therapy during the third trimester. Several authors have debated these findings.[38,63–76] In one study, 16 women were treated with insulin lispro and the remainder with regular insulin. None of the lispro patients had any ophthalmological changes during pregnancy.[65] In another study of pregnant type 1 diabetic women, 12 were treated with insulin lispro and 42 with regular insulin. None of the lispro-treated patients showed ophthalmological changes.[64] The development of diabetic retinopathy with the use of insulin lispro remains questionable. However, the likelihood is that patients' level of glycemia and not the drug is responsible for the proliferative retinopathy. A randomized trial with a substantial sample size may provide a definitive answer.

DOES INSULIN CROSS THE PLACENTA?

Academic scientists acknowledge that they often get things wrong. However, they also recognize that these errors sometimes get corrected over time since there are other researchers pursuing the same issues. However, the literature will confirm that this assumption for self-correction is often false. There are errors and misinterpretations of data in a lot more of the scientific papers being published and the guidelines emanating from them than anyone would normally suppose. For example, The Practice Bulletin no 137, August 2013, declared that *insulin does not cross the placenta.* The results of the above declarative statement give practitioners false confidence that they can freely administer insulin with potentially no harm to the fetus.

Various factors contribute to the problem of prolific distribution of questionable study results. There is a lot of scientific research that is poorly thought through, or executed, or both. Statistical mistakes are widespread, and most scientists are not statisticians. Some scientists use inappropriate techniques because those are the ones they are comfortable with; others experiment with new ones without understanding their refinements. Some just rely on the methods built into their software, even if they don't understand them. The peer reviewers who evaluate papers before journals commit to publishing them are much worse at spotting mistakes than they or others appreciate. Professional pressure,

competition, and ambition pressure scientists to publish more quickly than is prudent. The medical academic career structure that lays great pressure on publishing numerous papers aggravates all these problems. There is an academic price to pay for not getting published. The pervasive bias favors publication of claims to have found something new. By and large, scientists want surprising results especially when they are able to use these new data to reinforce current opinions and dogma.

Bauman and Yalow[77] demonstrated that beef and pork insulin unilaterally do not cross the placenta; they will, however, cross when complexed to insulin antibodies. Anecdotal cases have reported the presence of congenital anomalies with the use of insulin analogs. However, this unlikely finding still queries if insulin lispro and other analogs cross the placenta. Others found that in 51 infants of type 1 diabetic mothers, both animal and human, insulin crossed the placenta. The transfer was directly related to the level of anti-insulin antibodies in the mother.[78] In another study of 19 GDM women treated with insulin lispro, 4 of the subjects received intravenous infusion of the drug in labor; insulin lispro was not detected in the umbilical cord blood of their infants.[79] Holcberg et al.[80] using a perfusion model, reported that insulin lispro does not cross the human placental membranes at low concentrations. The maternal steady-state concentration reached 48 ± μU in the maternal artery and 28 ± 1 μU in the maternal vein, while in the fetal site insulin lispro was not detected. However, the concentration of insulin lispro in placental tissue was 1836 ± 220 μU. It has been shown that human insulin concentration in the fetus corresponds to peak serum insulin levels after doses of 14, 24, 104, and 278 units. This maternal dose is relatively common in the majority of GDM and type 2 women.[78] Insulin antibodies were detected in the cord blood of 95% of the offspring at birth. Others concluded that there was no appreciable transplacental transfer of either aspart or actarapid.[81,82] Boskovic et al.[41] evaluated 11 term human placentas from uncomplicated pregnancies immediately after delivery. Insulin lispro, at concentrations ranging from 100 to 1000 micro U/mL, was introduced into the maternal reservoir. The maternal side of the placenta was perfused with a constant concentration of lispro insulin; the fetal circulation was closed. Samples were drawn from both the maternal and the fetal circulations at regular intervals. The appearance of insulin lispro in the fetal circulation was analyzed by a specific radioimmunoassay. No placental transfer of lispro could be detected during perfusion with 100 and 200 μU/mL. In contrast, there was a concentration-dependent transfer to the fetus at ≥580 μU/mL, which corresponds to a maternal dose of approximately 75 units. This dose of insulin lispro is quite common in type 2 and obese GDM. Finally, they compared serum level and administered doses of lispro. Mothers treated with 50 units of insulin lispro achieved serum concentrations ≥200 μU/mL with an apparent linear correlation between dose and levels. The rate of placental transfer was 0.019 μU × min (−1) × g tissue(−1) at maternal levels of 580 μU/mL and 0.045 μU × min(−1) × g(−1) tissue at maternal levels of 1000 μU/mL. Moreover, a dose of 50 units may achieve serum concentrations >200 μU/mL with apparent linear correlation between dose and levels.[41] The author concluded that insulin lispro is not likely to cross the placenta at a single-standard dose and unlikely to reach or harm the unborn baby. However, they never took into consideration that the average type 2 GDM or type 2 diabetic women receive much higher doses of insulin than the authors assumed and, therefore, the fetus is exposed to insulin lispro in the majority of cases. Pollex et al.[83] reported that glargine in therapeutic concentration levels is not likely to cross the placenta based on a relatively low maternal dose. These studies clearly demonstrate that insulin crosses the placenta in a dose-dependent pattern.

Finally, the Cochrane Reviewers summarized their findings[84]:

> *Our analysis suggests only a minor benefit of short acting insulin analogs in the majority of diabetic patients treated with insulin. Until long-term efficacy and safety data are available, we suggest a cautious response to the vigorous promotion of insulin analogs. Due to fears of potentially carcinogenic and proliferative effects, most studies to date have excluded patients with advanced diabetic complications. For safety purposes, we need a long-term follow-up of large numbers of patients who use short acting insulin analogs. Furthermore, we need well-designed studies in pregnant women to determine the safety profiles for both the mother and the unborn child.*

We need to refrain from using the expression "unlikely to cross and/or harm the unborn fetus" because we are fostering misinformation. On the other hand, we need to remember that the majority of drugs cross the placenta. Thus, the question is not so much which drug crosses but which drug crosses and causes harm to the fetus?

THERAPEUTIC INSULIN REQUIREMENTS IN PREGESTATIONAL DIABETES

Type 1 diabetes is characterized as an inability to secrete insulin and type 2 diabetes and GDM have impaired insulin secretion and resistance, in addition to the physiological insulin resistance of pregnancy. The insulin requirements are not evidence of "physiological" need in diabetic patients but rather a reflection of the therapeutic dose of insulin required to achieve the established levels of glucose targeted by the physician.

Several prerequisites need to be addressed on the subject of therapeutic insulin requirements in pregnancy are as follows:

1. What level of glycemia does the care provider want to target? Since the normal glycemic profile in the nondiabetic pregnant woman is different than that of clinical thresholds targeted to optimize pregnancy outcome, different thresholds will require varying doses of insulin.
2. Is the method used to assess the level of glycemia accurate enough to reflect the true glycemic profile in the diabetic patient? Weekly blood glucose and HbA1C are not sensitive enough to demonstrate this association and only multiple glucose determinations throughout the day can provide the answer. Normal daily conditions rather than the hospital environment will provide the true level of glycemia that will mandate the insulin dose.[85,86]

Several studies have evaluated insulin requirements in pre-GDM.[87–89] The sensitivity to insulin changes throughout

pregnancy. In general, during the first trimester and even in the first half of the second trimester, there is a state of increased insulin sensitivity mainly due to the increased level of estrogen. Thereafter, due to the increased level of progesterone, human placental lactogen, prolactin, and other factors, there is a state of increased insulin resistance that, in turn, results in the need for increased insulin throughout pregnancy.

Jovanovic and Peterson[90] reported that there are increased insulin needs throughout pregnancy, 0.7 units/kg/d in the first trimester (weeks 5–12); 0.8 units/kg/d at week 18, 0.9 units/kg/d at week 26, and 1.0 units/kg/d at 36 weeks gestation. We[89] analyzed insulin requirements of type 1 and type 2 diabetic women using memory-based reflectance meters (SMBG) that reassured the accuracy of the glycemic control in all study participants. In both type 1 and type 2 diabetic subjects, we reported a triphasic insulin pattern. In comparison with type 1 patients whose daily insulin requirements were first trimester: 0.86 units/kg/d; second trimester: 0.95 units/kg/d; and third trimester: 1.19 units/kg/day, type 2 women required higher insulin doses during each trimester (first trimester: 0.86 units/kg/d, second trimester: 1.18 units/kg/d, and third trimester: 1.62 units/kg/d) (Figure 16-3). Our data were comparable to reports by other investigators.[87,88,90]

Although many insulin algorithms have been suggested for the management of the pregnant diabetic patient, the majority can only provide a basic guideline. It goes without saying that no algorithm or cook book approach can address the physiological/psychological needs of the human body. In addressing the needs of pregestational diabetic women, the care provider needs to assess, adjust, and customize the insulin dosage throughout pregnancy. In general, when insulin therapy is initiated, the total calculated insulin dose is based on the insulin requirements during a stage of pregnancy. For example, a type 1 diabetic patient during the second trimester who weighs 60 kg will require 57 units of insulin daily, 2/3s in the morning in a ratio of 2:1 (intermediate/rapid acting) and 1/3 in late afternoon/evening divided in a ratio of 1:1 (rapid acting with dinner and intermediate at bedtime). Further adjustment and the addition of insulin at lunchtime customize per patient needs.

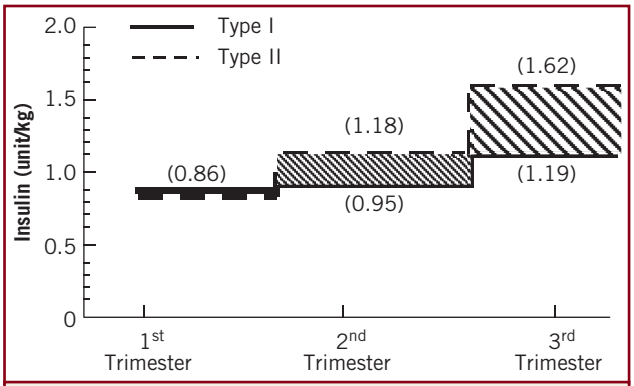

Figure 16-3 Triphasic pattern of insulin requirements by trimester of pregnancy for both type I and type II diabetes when corrected for weight. (Used with permission from Langer et al.[89])

Since the goal of therapy for type 1 diabetes is to mimic physiological insulin replacement, keeping in mind that there is a 24-hour requirement for basal insulin secretion, many advocate the use of insulin pumps (CSII) to approximate the insulin needs. The pump provides the basal insulin requirements and is especially effective during exercise and overcoming "the dawn phenomenon." However, the clinical experience with the insulin pump for type 1 diabetes in pregnancy to date is limited. Pump therapy requires that the patient be highly motivated, compliant and capable of calculating insulin dose; patient satisfaction for this subgroup appears to be high. Therefore, the only major limiting factor is the relatively high cost of the pump, which usually does not qualify for third-party reimbursement. Published data have reported that this therapy is as safe as multiple-injection therapy in achieving glucose control and perinatal outcome.[91]

GESTATIONAL DIABETES MELLITUS

The majority of women (over 90%), whose pregnancies are compromised by diabetes, are diagnosed with GDM. Approximately 9% of these women are undiagnosed type 2 diabetics.[92] Women who develop GDM often have higher insulin resistance already evident prior to conception, frequently in association with obesity. The beta cells are unable to increase insulin secretion as an adaptation to the decreased sensitivity. This may be a universal response to the insulin resistance since it is found in many ethnic groups.[93,94]

Women with a history of GDM have an increased risk to develop type 2 diabetes later in life. Therefore, many investigators refer to GDM and type 2 diabetes as the same disease with different names.[92] The reported risk ranges from 6.8% to 92% when impaired glucose tolerance test is combined with overt diabetes and 3% to 50% for overt diabetes alone.[95,96] Approximately 56% of GDM women will require pharmacological therapy. The options are either oral antidiabetic drugs or insulin. To identify the GDM women who need pharmacological therapy, the following questions need to be addressed.

Who Needs to Get Insulin Therapy?

When diet therapy fails to achieve established levels of glycemic control, insulin and antidiabetic agents are the validated treatment options. In GDM, opinions of authoritative bodies differ regarding the threshold of fasting plasma glucose for the initiation of pharmacological therapy (glyburide or insulin). Several surveys have been performed in the United States to evaluate physician practice.[97–99] Landon et al.[97] reported that 11% of the participants initiated insulin treatment at fasting plasma values of 90 to 104 mg/dL; 54% at fasting of 105 mg/dL; 23% at a threshold fasting of 110 to 119 mg/dL; and 9% at fasting levels in the range of 120 to 150 mg/dL. Only 22% of the survey respondents used 120 mg/dL as the postprandial threshold for insulin initiation; the remaining 78% used values ranging from 121 to 160 mg/dL. Subspecialists reported mean fasting and postprandial thresholds of 105.1 ± 7.0 and 138.7 ± 15.3, respectively. A review of the literature of the past two decades[86] reveals that the majority of authors used a fasting plasma threshold of 95 to 105 mg/dL and a postprandial threshold of >120 to 130 mg/dL. Despite these criteria, the majority of the studies reported a relatively high rate of macrosomia and LGA infants.

The majority of fasting and postprandial plasma glucose thresholds in use are not based on peer-reviewed studies but rather on clinical opinions. Additional controversy addresses the use of the 1- and 2-hour postprandial determinations. Therefore, it is surprising that only one set of criteria is recommended as the glucose target to optimize pregnancy outcome in light of the fact that there are so many reported thresholds. The Fourth International Workshop on Gestational Diabetes, the North American Diabetes in Pregnancy Study Group, and the American College of Obstetrics and Gynecology all recommended a threshold of ≥95 mg/dL,[100–103,105,106] whereas others recommended ≥105 mg/dL.[100,104]

It is the author's opinion that using a fasting plasma glucose threshold >95 mL/dL will decrease rates of macrosomia and LGA infants. This is based on a large prospective study[105,106] demonstrating that the rate of LGA was similar with either diet or insulin therapies when fasting plasma from the oral glucose tolerance test (OGTT) was <95 mg/dL. In contrast, in patients with fasting plasma between 95 and 105 mg/dL, the rate of LGA was threefold higher (27%) in diet versus insulin-treated subjects (Figure 16-4).

Most authorities agree on initiation of drug therapy with elevated postprandial values ≥120 mg/dL for 2 hours or ≥130 to 140 mg/dL for 1 hour. Using the above fasting plasma standards and the postprandial criteria, approximately 30% to 50% of women with GDM will require pharmacological therapy when diet therapy alone fails to reduce glycemic levels. These thresholds are probably too high; it will not be surprising if in the future lower thresholds are used as the cutoff. In a recent study using continuous blood glucose measurements, we found that the maximum excursion of the postprandial glucose level occurred after 90 minutes and reached glycemic levels of 110 mg/dL in nondiabetic pregnant women.[107] However, this glycemic profile in nondiabetic subjects still needs to be validated in association with pregnancy outcome.

Using the Bergman Minimal Model, patients who qualified for diet therapy were evaluated; only those who achieved established levels of glycemic control improved insulin secretion and sensitivity. Patients who failed to achieve glycemic control, although exhibiting slightly improved sensitivity, did not achieve the same level of insulin response and sensitivity as nondiabetic women. Furthermore, using the same methodology,

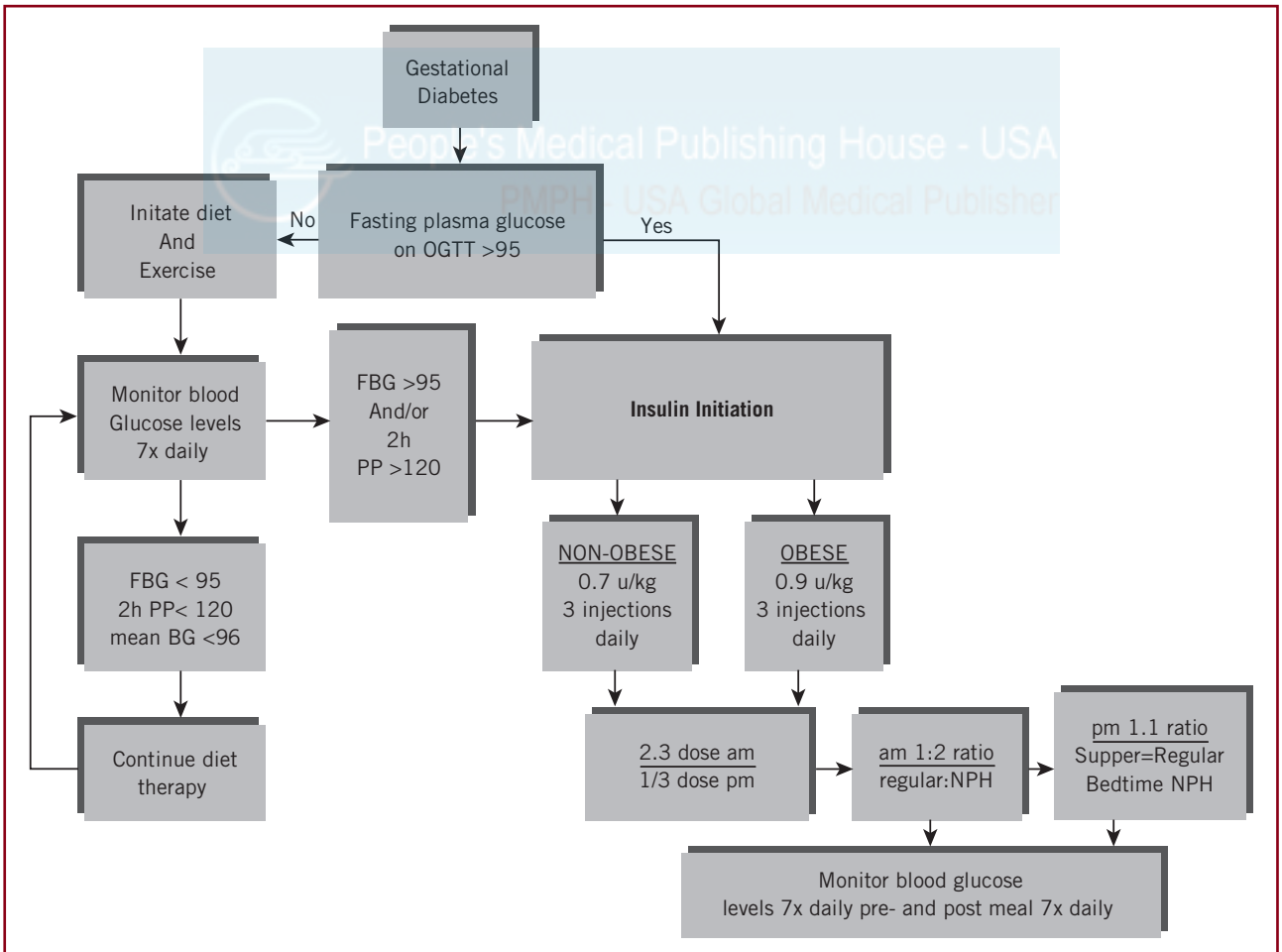

Figure 16-4 GDM: insulin initiation. (Modified from Langer.[105])

stratifying the diabetic women into two groups of above and below 95 mg/dL, we found that the lower fasting group improved their primary lesion significantly compared to the other group.[108] In another study, we demonstrated that women with fasting plasma <95 significantly improved glycemic levels, whereas those with fasting >95 failed. Thus, the data suggest that pharmacological therapy should be initiated at fasting levels <95 order to maximize pregnancy outcome.[109]

Can the Fetus Itself Provide a Marker for Pharmacological Initiation?

The main therapy in GDM is to prevent fetal complications. Therefore, it would be beneficial if the fetus could be used as the marker for initiation of pharmacological therapy rather than treating a large group of mothers of whom 30% will demonstrate neonatal morbidity. Weiss et al.[110,111] suggested the use of amniotic fluid insulin at 29 weeks gestation as a marker for insulin initiation. Measurement of the fetal abdominal circumference (>70–75th percentile) early in the third trimester has also been suggested as a marker for insulin initiation to prevent macrosomia. A few studies primarily in pregnancies with maternal fasting glucose levels of <105 mg/dL have evaluated this approach. The measurement of both maternal and fetal factors may eventually enhance fetal outcome in a subset of GDM patients.[112]

An opposite approach was proposed by Coustan and Imarah[113] who suggested treatment of all GDM women with insulin as a prophylactic approach, which may decrease fetal morbidity. Using this approach will commit all GDM women to insulin therapy and will increase the rate of women treated unnecessarily with pharmacological therapy.

Although the methods of using the fetus as a marker in his/her own therapy is attractive, a few limitations are apparent. Fetal insulin is metabolized mainly in the liver and, therefore, the insulin level found in the amniotic fluid will not identify all hyperinsulinemic fetuses but rather only the severely ill ones. We[114] compared 38 pregnant diabetic subjects for insulin levels in the umbilical cord at delivery and amniotic fluid within 1 day of delivery. By utilizing the Hollister U-Bag, first void neonatal urine was collected to validate the amniotic fluid insulin values. Insulin levels were measured using the radioimmune assay double antibody technique (coefficient of variation = 4.408). The fetal cord blood insulin level was twofold higher than neonatal urine insulin level (24.5 ± 9 vs. 11.8 ± 5, $P < .05$) and fourfold higher than amniotic insulin levels (23.4 ± 4 vs. 6.8 ± 0.7, $P < .01$, respectively). A positive association was found between amniotic fluid insulin levels and neonatal urine insulin ($r = 0.55$) and fetal serum insulin ($r = 0.42$). Our data suggest that amniotic fluid insulin is of fetal origin but represents only the most severe hyperinsulinemic fetuses. The use of amniotic fluid as a diagnostic tool for an abnormal fetus will result in a high false negative rate.

Regarding abdominal circumference, it is well known that most fetal growth occurs in the third trimester and the growth, especially in diabetic patients, is influenced by environmental factors (nutrition and glucose). Furthermore, studies have failed to demonstrate that a given gestational age, early in the third trimester, can predict fetal weight at delivery. Therefore, a snapshot approach at 28 to 29 weeks gestation may result in under estimation of the potential fetal disease. A combination of maternal criteria at entry (fasting and postprandial) and throughout pregnancy, and a blood glucose profile in association with ultrasound examination will provide a more customized approach. For example, a fetus with an abdominal circumference of 68 at 29 weeks gestation but with an elevated fasting plasma and/or postprandial glucose whose mother cannot achieve targeted levels of glycemic control will benefit from pharmacological therapy. On the other hand, a fetus with an abdominal circumference of 25, even with an abnormal glycemic profile, may not weigh above the 90th percentile at delivery. The question that still needs to be answered is the effect of excessive fetal growth within the norm (11th–89th birth percentiles). For example, a fetus that is expected to match growth for the 15th percentile surpasses that growth to the 80th percentile because of the effect of the diabetes. This situation would most likely be associated with adverse outcome.

How Long Should a Patient Remain on Diet Therapy Before the Introduction of Pharmacological Treatment?

Although opinions and regimens proliferate, there is a lack of consensus and hard data on how long a pregnant diabetic woman should remain on diet before initiation of pharmacological therapy. To date only a single study evaluated the time required to achieve desired levels of glycemic control with diet alone during a four-week study period. Seventy percent of the subjects with initial fasting plasma glucose <95 mg/dL achieved targeted levels of glycemia within a two-week period with no significant improvement thereafter.[109] The failure to initiate a timely introduction of insulin therapy may lead to fetal hyperinsulinemia and associated complications. However, premature initiation of insulin therapy to the patient who could have achieved glycemic control with diet alone may cause unnecessary drug treatment. In cases of GDM in which a diagnosis is made after 30 to 33 weeks of gestation and there is scant time available to affect the desired level of control, initiation of pharmacological therapy is recommended. There is greater flexibility in treatment modalities when GDM is diagnosed early in the third trimester.

INSULIN REQUIREMENTS IN GDM

What is the required dose to achieve the established level of glycemic control? The paucity of information regarding insulin requirements in GDM stems from the fact that most studies of diabetes in pregnancy have been conducted on subjects with pre-existing diabetes. We[115] in a prospective study evaluated GDM women who underwent an OGTT six to eight weeks postpartum to exclude all undiagnosed type 2 patients. To ascertain the correct insulin dose needed to achieve targeted levels of glycemic control, we used memory reflectance meters to obtain accurate and reliable verified glucose data. Fifty-seven patients with a normal OGTT postpartum were included in the study. Insulin requirements demonstrated a biphasic pattern. The first phase, 24 to 30 weeks gestation, was characterized by a significant weekly increase in insulin dose to maintain the targeted levels of glycemic control. In the second phase, from 31 to 39 weeks, the level of glycemic control remained constant without the necessity to alter the insulin dose (Figures 16-5 and 16-6). Insulin requirements for obese patients were 0.9 units/kg and 0.8 units/kg for nonobese subjects.

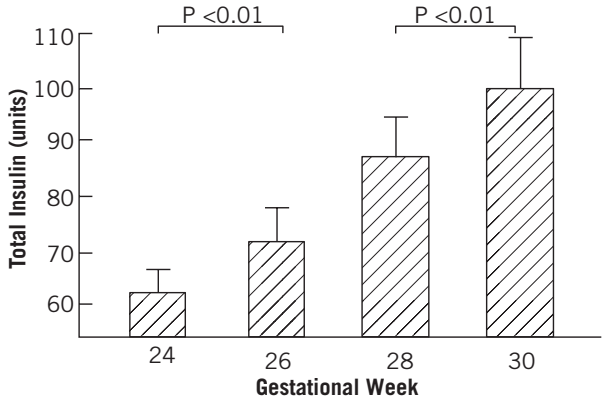

Figure 16-5 Insulin requirements in Gestational Diabetes (GDM). (Used with permission from Langer et al.[115])

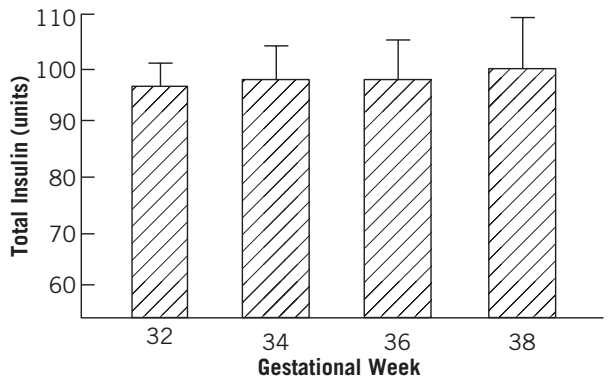

Figure 16-6 Insulin requirements in gestational diabetes mellitus.

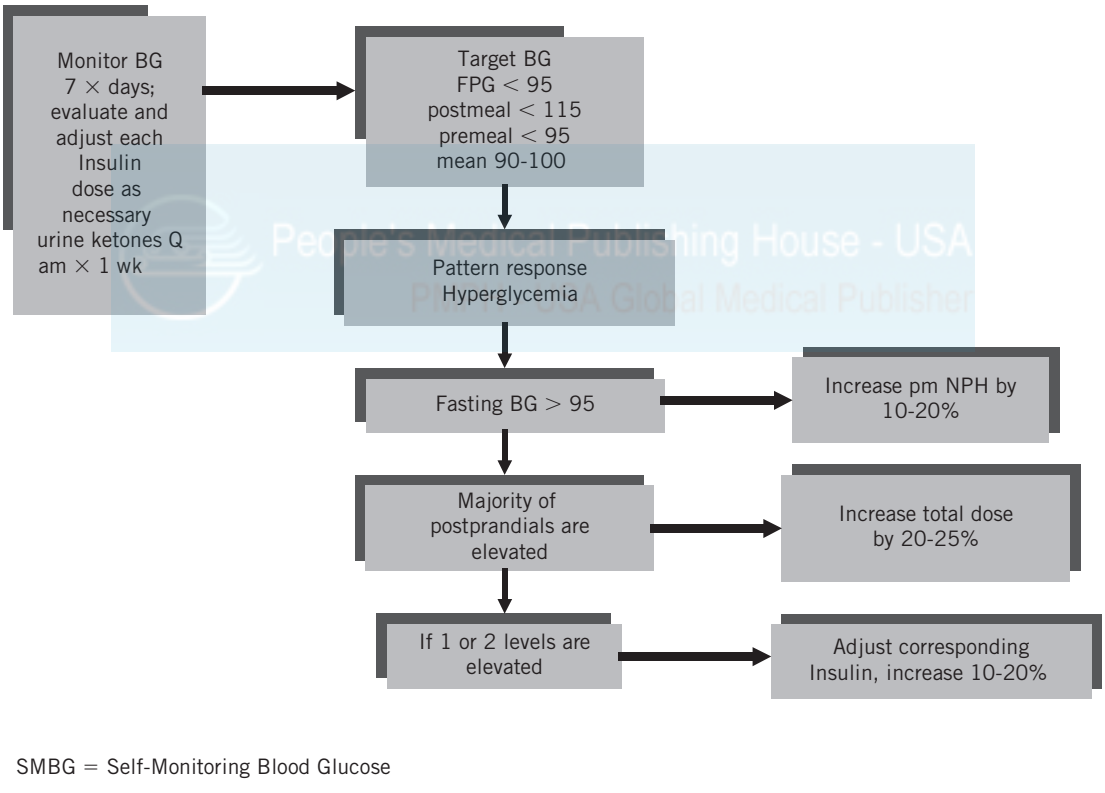

Figure 16-7 Insulin adjustment to hyperglycemia pattern.

There was a significant difference in variability measured by the coefficient of variation (45% vs. 25%, $P < .01$), respectively.

The total insulin dose required to reach the established level of glycemic control for the majority of patients range from 40 to 90 units (body-weight dependent). For the GDM patient during the first phase, it is beneficial to schedule frequent visits to adjust insulin dose to maximize glycemic control. During the second phase, the care provider is vigilant about fetal growth and surveillance in addition to blood glucose testing although a significant increase in insulin dose is not anticipated.

The insulin to be administered should be calculated in a similar pattern as that recommended for type 1 diabetic patients. The insulin is divided into three doses: regular and intermediate-acting insulin in the morning; regular at dinner; and intermediate acting at bedtime. The standard formula for the amount of insulin prescribed should be 2/3s of all insulin in the morning (2:1, intermediate acting: regular)

and 1/3 in the evening (1:1 regular [dinner]: intermediate acting [bedtime]). If after three days of self-monitoring blood glucose levels with insulin administration the overall glycemic profile fails to reach targeted levels, insulin should be increased at the rate of 15% to 20% for each dose. The procedure is repeated with a 10% to 15% increase in overall insulin dose. Thereafter, alteration in insulin dose is based on achievement of glucose target ranges for overall, preprandial, and postprandial levels (Figures 16-6, and 16-7).

In summary, insulin therapy should mimic as much as possible the physiological pattern of insulin secretion. Although different kinds of insulin are on the market today, no specific type (from human to analog) has demonstrated a better overall effect. When a pregnant woman is treated with insulin, the care provider needs to take into account the presence of insulin resistance that requires a relatively high insulin dose to overcome the abnormal glycemic profile. Overall, insulin requirements after two weeks of insulin therapy increase by 26% for type 1 diabetes; 34% for type 2 diabetes; and more than 40% for GDM from the calculated dose at entry to the actual dose that maintains targeted levels of glycemic control. Pregnancy provides a relatively narrow window of opportunity to prevent fetal complications. Therefore, an intensified approach in insulin management should be the goal.

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Exercise

The Logical Intervention for Diabetes in Pregnancy

17

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All truly great thoughts are conceived while walking.

—Friedrich Nietzsche

Key Points

- American College of Obstetricians and Gynecologists (ACOG), American Diabetes Association (ADA), and American College of Sports Medicine (ACSM) endorse physical activities as an adjunctive intervention to prevent and manage gestational diabetes.
- Exercise involving large muscles increases glucose uptake 35- to 40-fold, resulting in three to four times increase in total body glucose uptake.
- To benefit from an exercise program, patients with gestational diabetes should engage in a daily routine of 30–45 minutes of moderate physical activity.

Industrialized countries are currently experiencing an epidemic of obesity and a rising incidence of diabetes. In the United States alone, it is estimated that more than one-half of the adults are either overweight or obese.[1] Pregnancy has become a major contributor to this epidemics; sedentary lifestyle and obesity are key etiologic factors in the development of gestational and type 2 diabetes. The Diabetes Prevention Program (DPP) has demonstrated in nonpregnant adults and by now well established that a lifestyle intervention (exercise and diet) was more effective in preventing the development of type 2 diabetes than medical (metformin) intervention.[2] Pregnancy is a unique time for behavior modification and a period during which women may be more prone to adapt healthy lifestyle habits that they may continue beyond pregnancy.[3]

Historically, diabetes was considered a contraindication to exercise in pregnancy. Many women with gestational diabetes mellitus (GDM) failed nutritional therapy and it was reported that 39% required insulin to optimize pregnancy outcome.[4] In 1985, data were presented[5] at the Second International Workshop-Conference on gestational diabetes, which contributed to the first recommendation that mothers with GDM who maintain an active lifestyle may continue a program of moderate exercise under medical supervision.[6] It was reported that, for most women with GDM, exercise is a safe and effective alternative therapeutic intervention, which precludes the need for medical therapy. However, only 15.8% of all pregnant women follow the ACOG physical activity guidelines[7] and 61% participate in some form of exercise,[8] slightly higher compared with 10% adults who meet the Physical Activity Guidelines for Americans in accordance with the National Health and Nutrition Examination Survey.[9]

Exercise has long been accepted as a complementary intervention in the prevention and management of diabetes in nonpregnant adults. The ADA recommends adults with diabetes engage in at least 150 min/wk of moderate-intensity aerobic activity (50%–70% of maximum heart rate by age) distributed over at least three days each week with no more than two consecutive days without exercise.[10] Furthermore, for prevention of type 2 diabetes, the ADA recommends lifestyle changes that include weight loss (7% body weight) and regular physical activity (150 min/wk). Lifestyle interventions for the prevention or management of diabetes have also been endorsed, recommended, and reaffirmed by the ACOG, the ADA, and the ACSM.[11,12] During pregnancy, in the absence of medical or obstetrical contraindications, ACOG recommends women engage in 30 minutes or more of moderate-intensity physical activity during most, if not all, days of the week. For women with gestational diabetes, AGOG and the ADA have endorsed exercise as "a helpful adjunctive therapy" in treatment of the disorder.[13] However, exercise protocols for women with GDM are not widely prescribed despite the endorsement by these professional organizations.

A limited number of randomized controlled trials have been conducted to evaluate the effect of exercise on preventing GDM or as an adjunct intervention to manage GDM[14]; the results reported in the literature are mixed and the literature inconclusive; however, the potential short- and long-term benefits are well recognized.

Pregnancy has been characterized as a diabetogenic state brought about by changes in hormone levels (estrogen, prolactin, human chorionic somatommotropin, human placental lactogen [HPL] aka human chorionic somatomammotropin [HCS], cortisol, and progesterone) that lead to insulin resistance and increased insulin requirements in diabetic subjects. In pregnant women, catabolic stress hormones trigger an increase in fuel metabolism that results in wide glycemic shifts between the fasting state[15] when glucose levels are lower and the fed state when they are higher. There is an increase in hepatic gluconeogenesis throughout gestation that is modulated by an increase in insulin secretion. However, despite counter-regulatory processes, patients with GDM have impaired insulin sensitivity that results in decreased glucose uptake by muscles and splanchnic organs. These patients experience adipocyte hypertrophy and increased fat storage (Figure 17-1).

Pregnancy-induced insulin resistance predisposes subjects who have risk factors, such as obesity, to the onset of pancreas β-cell dysfunction and gestational diabetes. As many as 60% of women with GDM will develop type 2 diabetes within four years after delivery.[16] It is well established that exercise and weight loss improve insulin sensitivity and could prevent or reduce the risk of GDM. Increased glucose uptake by skeletal muscle is partly attributable to increased muscle perfusion during exercise. Exercise leads to beneficial alterations in body composition and biochemical, physiological, and morphological changes in skeletal muscles. Exercise in an obese woman leads to weight loss and the percentage of type 1 muscle fibers increases, resulting in increased muscle oxidative capacity.[17,18] This capacity in turn allows to burn more fat throughout the day and improves weight control. In addition to these factors, exercise may relieve stress, reduce anxiety, and depression, and improve self-confidence and, in doing so, limit "emotional eating" that contributes to weight gain and insulin resistance. The metabolic relationship between exercise and nutrition is complimentary. Increased physical activity often leads to improvements in self-image and other factors that, in turn, support healthy life style.

After an exercise session, glucose tolerance is *improved* for variable periods depending on the mass of the muscle activated, duration, intensity, and insulin response.[19] A large contracting skeletal muscle can increase the oxidative process by a factor of 50 and its glucose uptake 35- to 40-fold, leading to a total body glucose uptake that is up to four times higher. Essential to this process that results in improved insulin sensitivity and glucose uptake is the activation of particularly large muscles such as the quadriceps. Many exercise programs designed to achieve euglycemia fail because either large muscle groups were not activated or the duration or intensity of the exercise routine was too limited.

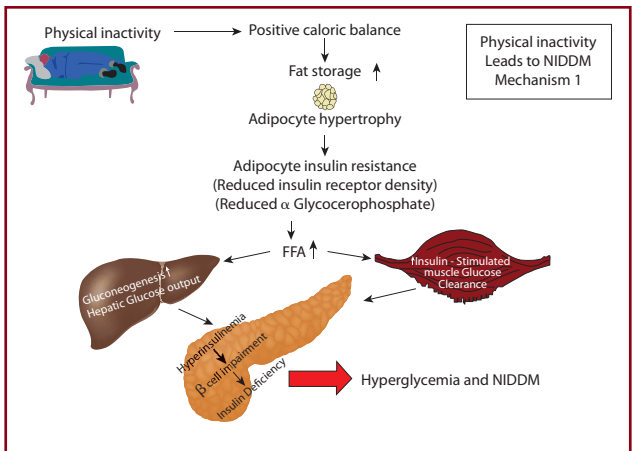

Figure 17-1 Physical inactivity leads to hyperglycemia and type 2 diabetes mellitus.

EXERCISE IN PREGNANCY

Historically and until the mid-1980s, diabetic pregnant patients were recommended to rest during pregnancy, and pregnancy was not considered an appropriate time for initiating an exercise program for any pregnant woman. There has long been concern that exercise during pregnancy may increase the risk of preterm delivery, fetal growth restriction, or fetal distress due to a decrease in the uterine blood flow during exercise that could affect the fetus and result in an abnormal fetal heart rate and other physiologic responses that may be harmful to the fetus or even result in fetal demise. In fact, there is no evidence to support these concerns, nor is there evidence that the hyperthermia that may occur during moderate-intensity exercise early in pregnancy is teratogenic.

For determining an exercise prescription, the ACSM recommended using VO_2 max (maximal oxygen consumption) and most recently VO_2R (VO_2 Reserve). VO_2 Reserve is obtained by subtracting resting VO_2 from max VO_2. In the clinical setup, this is not practical. In the nonpregnant woman, target heart rates were frequently used to prescribe exercise.

In regard to prescribing exercise intensity, however, it should be recognized that during pregnancy maximal maternal heart rate reserve decreases and resting heart rate increases. Target heart rate zones revised for pregnancy may be used to measure exercise intensity or it may be more practical in the clinical setup to use Borg's rating of perceived exertion (RPE). The Borg scale ranges from 6 (extremely light) to 20 (extremely hard). Pregnant women may begin exercise at a moderate RPE of 12–14 and increase the intensity of exercise to 15 or 16 with conditioning. The "talk test" may be more practical to use to avoid overexertion.[20]

Given the common pathophysiology of GDM and type 2 diabetes, it is logical that a higher level of physical activity prior to pregnancy and early in the gestation could decrease the risk of GDM.[21] Exercise is beneficial for most pregnant women for the prevention of GDM, but it is particularly beneficial for overweight and obese women and those who have a prior history of GDM, a first-degree relative with diabetes, or other risk factors for the development of carbohydrate intolerance during pregnancy.[20]

While contact sports and heavy weight lifting are discouraged during pregnancy because of potential for injury, many activities could be safely continued in pregnancy.[20] Physiologic changes that may alter a pregnant women's response to exercise should, however, be recognized. Just as prolonged fasting in pregnancy is discouraged because it may challenge glycogen energy reserves and result in deleterious effects on the growth and developing fetus,[22] exercise that is excessive or coupled with inadequate nutrition has the potential to cause harm. In the nonpregnant state, there is a hypoglycemic response to sustained exercise. Prolonged exercise in pregnancy could also lead to hypoglycemia (Figure 17-2).[23] With prolonged exercise free fatty

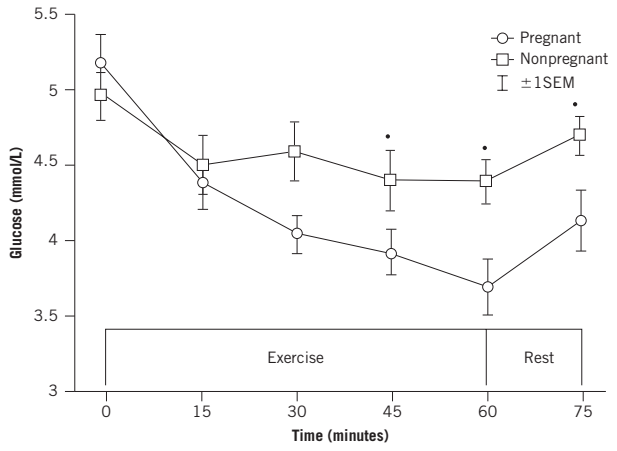

Figure 17-2 Glucose concentrations during prolonged exercise: pregnant versus nonpregnant women. (From Soultanakis et al.[23])

acid and ketone levels rise as glucose levels fall. Hypoglycemia may also result when a pregnant woman exercises and her glucose level is depressed secondary to fasting or medication. The risk of hypoglycemia is greatest in early pregnancy, prior to the fall in insulin-mediated glucose disposal that occurs over the course of the second and third trimesters. In the presence of ketonuria, patients should not exercise. Diabetic patients who are also medically treated should measure blood glucose prior to exercise and increase carbohydrate following guidelines: For blood glucose below 120 mg/dL, ingest 15 g of carbohydrate prior to exercise and 30 g for every 60 minutes of exercise. For blood glucose of 120–130 mg/dL, ingest 30 g for 60 minutes of exercise.

Over the past 30 years, our laboratory has conducted studies examining the impact of pregnancy on maternal and fetal responses to exercise, on the regulation of glucose homeostasis by glucagon, insulin, and catecholamines and other.[5,22–26] The results of these studies led to the establishment of safe exercise regimens for both diabetic and nondiabetic pregnant women.[24] At an intensity of 55% of maximal oxygen consumption (VO_2 max), we observed a rapid reduction in both glucose and insulin concentrations with as little as 15 minutes of exercise (Figure 17-2). After 45 minutes, glucose concentration declined further, suggesting that at this point the potential risk of hypoglycemia with moderate-intensity continuous exercise may rise.[23]

When designing an exercise regimen for a pregnant woman, the baseline conditioning status should be taken into consideration (Table 17-1). Given that a sedentary lifestyle is a risk factor for diabetes and obesity, most women who have pregestational diabetes or develop GDM are deconditioned. Preexisting and pregnancy-induced low-back pain and joint pain are also common concerns. Pregnant women with these limitations may be more tolerant of nonweight-bearing exercise. We have demonstrated by indirect calorimetry that, when compared to weight-bearing exercise at submaximal levels, there is preferential carbohydrate use during nonweight-bearing exercise in pregnancy,[25] primarily because of the ability to sustain more prolonged and sustained level of exercise. The ADA 2013 issued and reaffirmed recommendations for primary prevention of diabetes: "Among individuals at high risk for developing type 2 diabetes, structured programs that emphasize lifestyle changes that include moderate weight loss (7% body weight) and regular physical activity (150 min/wk)."[27]

PHYSICAL ACTIVITY AND GESTATIONAL WEIGHT GAIN

A 2013 systematic review and meta-analysis that included nine randomized controlled trials with nonpregnant patients at risk for diabetes concluded that comprehensive lifestyle interventions in nonpregnant studies, which include exercise and dietary interventions, result in weight loss and decrease in the incidence of type 2 diabetes in nonpregnant subjects at the end of intervention and up to 10 years.[28] However, historically there was reluctance to limit weight gain in pregnancy.

There are few studies in pregnancy combining diet and exercise; however, evidence is emerging that both exercise and weight restrictions are safe interventions in overweight and obese pregnant women.

The 2009 Institute of Medicine (IOM) recommendations for weight gain in obese pregnant women have not been universally accepted and have come into questions since additional gestational weight gain as recommended to obese mothers further aggravates the preexisting obesity.[29] Obesity and additional weight gain have been recognized as independent risk factors for maternal and fetal complications of pregnancy with significant life-long consequences.

In 2013, ACOG has published a committee opinion stating that "For an obese pregnant woman who is gaining less weight than recommended but has an appropriately growing fetus, no evidence exists that encouraging increased weight gain to conform with the update IOM guidelines will improve maternal or fetal outcomes."[30]

Excessive gestational weight gain significantly increases the risk of GDM and a number of other adverse perinatal outcomes as well as the risk of postpartum weight retention and obesity.[31] More than one-third of young (age 14–25), low-income, ethnic minority women move to a higher body mass index (BMI) category within one-year postpartum.[32] Pregnancy is an opportune time to target weight management and address the rapidly increasing prevalence of obesity in the population. A triad of pregravid obesity, excessive gestational weight gain, and diabetes in pregnancy are often found in combination. Each of these factors independently increases the risk of fetal overgrowth and, in turn, childhood obesity.[33] Excessive gestational weight gain thereby plays a vital role in the development of obesity and obesity-related complications in women and their offspring.

The IOM in 2009 has recommended that underweight women (BMI < 18.5 kg/m^2) gain 28 to 40 lbs, normal weight women (BMI 18.5–24.9 kg/m^2) 25 to 35 lbs, overweight women (BMI 25.0–29.9 kg/m^2) 15–25 lbs, and obese women (BMI ≥ 30.0 kg/ m^2) 11–20 lbs in pregnancy. It did not make specific recommendations for individual obesity classes, and there has been considerable controversy over gestational weight gain targets for those with severe obesity. In our experience, minimally to no weight gain in obese women has no deleterious impact on the fetus and is beneficial to the mother in regard to her long-term

TABLE 17-1 Exercise Prescription for Sedentary, Overweight, or Obese Women With GDM Who Are Unaccustomed to Exercise[20]

Previously Sedentary and/or Overweight/ Obese Pregnant Women	% HRR	% VO2 R	RPE	Target Exercise Energy Expenditure (MET-h/wk)
Weeks 1–3 of training (26 wk gestational age)	35–39	40–45	12–14	>16
Weeks 3–6 of training (gestational age 29 wk)	45–55	50–60	13–15	28
Weeks 6–9 of training (gestational age 32 wk)	60	65	15–16	28
Weeks 1–3 of training (gestational age 35 wk)	60	65	15–16	28

Abbreviations: GDM, gestational diabetes mellitus; MET, metabolic energy equivalent task; % HRR, heart rate reserve; % VO_2 R, VO_2 Reserve; RPE, rate of perceived exertion from 6 at rest to 20 at maximal exertion.

% HRR = %VO_2 R is different for obese or pregnant subjects. It is higher by about 5% compared to % HRR until 70% VO_2R, after which % VO_2R and % HRR are about equal.

weight loss goals.[34,35] As for glycemic control in women with diabetes, we recommend adjusting physical activity and diet in relation to gestational weight gain.

No studies have been conducted to compare limiting weight gain to exercise in pregnancy and determine which intervention is more effective in reducing GDM.

Many of the individual trials that have investigated the impact of physical activity on gestational weight gain have been limited by their small size and poor participant compliance. The modest nature of a number of the interventions studied and the relatively late timing of their initiation are other common factors that have likely limited the studies' ability to find a significant reduction in gestational weight gain. Recognition of these limitations have prompted a 2011 meta-analysis of 12 physical activity intervention trials that collectively enrolled over a thousand women.[36] All of the included trials reported gestational weight gain as a secondary outcome. The analysis uncovered a modest but statistically significant reduction in gestational weight gain among those exposed to various physical activity interventions. Although the 0.6 kg difference reported is of minimal clinical significance on the individual level, given the obesity and diabetes epidemic even a small reduction deserves notice from a population standpoint. As stated earlier for primary prevention of diabetes, the ADA[27] recommends that among individuals at high risk for developing type 2 diabetes, structured programs that emphasize lifestyle changes that include moderate weight loss (7% body weight). In a 2013 population-based historical study of 66,010 obese pregnant women, we have found that for women who have gained ≤2 pounds (including weight loss), there was no significant risk of small-for-gestational-age infants, one of the historical concerns, and most significantly associated with a decreased risk for large-for-gestational-age infants, a common complication of gestational diabetes[35]; this findings reinforce that ACOG committee opinion that for an obese pregnant woman who is gaining less weight than recommended but has an appropriately growing fetus, no evidence exists that encouraging increased weight gain to conform with IOM guidelines will improve maternal for fetal outcomes.[30]

PHYSICAL ACTIVITY AS A LIFESTYLE INTERVENTION TO PREVENT GDM

For exercise to be effective in improving glycemic control, it is important that it involved activation of large muscle groups and is of sufficient duration and intensity.[17] Energy expenditure for a given activity can be quantified using its metabolic energy equivalent task value. These values range from 0.9 for sleeping and 1.0 for being seated at rest to 23 for running at a speed of approximately 4 miles per hour. Dempsey et al. reported that compared with inactive women, women who participated in any physical activity during the year prior to pregnancy experienced a 56% GDM risk reduction. Women who spend more than 4.2 h/wk exercising experienced a 74% GDM risk reduction (Table 17-2). Women who engaged in physical activity during both time periods experienced a 69% GDM risk reductions.[37]

A 2011 meta-analysis of 7 prepregnancy and 5 early pregnancy studies included 34,929 and 4401 participants, respectively.[38] Pooled odds ratios (ORs) were calculated by comparing the risk of GDM in those with the highest versus the lowest level of physical activity. Exercise in early pregnancy was associated with a 24% lower risk of GDM (pooled OR 0.76, 95% confidence interval [CI] 0.70–0.83) and exercise prior to pregnancy with a 55% lower risk (pooled OR 0.45, 95% CI 0.28–0.75). That meta-analysis included five prospective cohort, two retrospective case-control, and two cross-sectional studies. No randomized clinical trials meeting the authors' inclusion/exclusion criteria were identified at that time.

In 2012, Stafne et al. reported the results of a randomized trial that included 855 women with normal BMIs.[39] A 12-week exercise program that included weekly 1-hour group exercise sessions and a 45-minute twice-weekly home exercise program was initiated at 20 weeks of gestation. A similar percentage of women in the intervention and control groups developed GDM (7% and 6%, respectively), and no difference in insulin resistance was detected. This suggests that an exercise program, although beneficial to all is more effective in preventing gestational diabetes in overweight or obese women, rather than in normal weight women. This 2012 trial was the largest of six that were included in a recent meta-analysis[40] that was limited to randomized trials that investigated the association between physical activity in pregnancy and GDM. The other five trials were initiated earlier in pregnancy but the majority if not all the various interventions were carried out in the second and third trimesters, and the power of the trials was limited by their small size, ranging from a total of 41 to 142 participants. No significant difference in the risk of GDM was detected. Only one of the studies included in this 2013 meta-analysis limited enrollment to obese pregnant women.

Utilizing a population-based birth registry in central New York from the mid-90s, we previously found lack of physical exercise to be associated with higher rates of GDM among women with a BMI ≥ 33 (OR 1.9, 95% CI 1.2–3.1; Figure 17-3).

This study demonstrated that for obese pregnant women with BMI above 33 engaging in physical activities of any kind reduces the risk of GDM in half.[41]

Oostdam et al. attempted to investigate the impact of an exercise intervention program on the risk of GDM among women with a BMI greater than 25 and either a history of GDM or macrosomia or a first-degree relative with diabetes. The intervention involved twice weekly 60-minute aerobic and strength exercise sessions that began around 15 weeks of gestation. The number of women developing GDM in the exercise versus the control group was not significantly different but only 16% of the women in the intervention group attended at least half of the exercise sessions.[42]

Most women with type 1 diabetes in pregnancy have been managing their disease since childhood and are quite comfortable with their typical glycemic response to activity outside of pregnancy. It is crucial that they are adequately educated regarding their increased risk of exercise-induced hypoglycemia in pregnancy. That risk is largely due to decreased hypoglycemic awareness and counter-regulatory adaptations that may be altered by pregnancy-related augmentation of catecholamine and glucagon responses. For these women, even routine daily activity (household chores, shopping, etc.) can result in severe hypoglycemia if that activity is not accurately factored into insulin dosing and carbohydrate. These patients are also prone to ketoacidosis. The widespread use of insulin pump devices and growing popularity of continuous glucose sensors may facilitate and increase the safety of exercise for pregnant women with type 1 diabetes. Nonetheless, we recommend that these patients engage in moderate exercise limited to 30 minutes per session.

Although the risk of hypoglycemia with gestational and type 2 diabetes is substantially lower, these women often enter pregnancy obese and deconditioned and for this reason are at higher risk of exercise-related musculoskeletal injuries.

The type, intensity, and frequency of the exercise interventions studied in these trials may have been inadequate to improve perinatal outcomes. As demonstrated by Lesser et al., in a small randomized cross-over design study, one single bout of exercise session is insufficient to blunt the glycemic response to a mixed nutrient meal.[43] A single bout of exercise and regular physical activity enhance insulin sensitivity. Insulin and exercise stimulate muscle glucose uptake. A single bout of exercise increases insulin sensitivity primarily in the muscles activated from hours to 48 hours.[44] However, for both prevention and management of diabetes, these patients should engage in at least 150 minutes of exercise per week, at least 30 min/d preferably after meals. In our experience, an average of 7–10 days is required to achieve glycemic control among obese sedentary pregnant diabetic women.[45]

Despite the limited evidence outlined, for women with GDM and type 2 diabetes, any increase in exercise, particularly postprandial activity, is generally recommended secondary to its beneficial impact on postprandial hyperglycemia, weight gain, and insulin requirements. In addition, pregnancy is a period during which most women are highly motivated by concern for the welfare of their child. Their frequent interactions with health-care providers during pregnancy should be recognized as an opportunity to provide education and encourage lifestyle changes that

TABLE 17-2 GDM Risk in Relation to Physical Activity

Physical Activity	Risk Reduction (%)	RR	95% CI
Any (prior)	56	0.4	0.21–0.91
≥ 21 METs/wk	74	0.26	0.1–0.65

Abbreviations: CI, confidence interval; GDM, gestational diabetes mellitus; MET, metabolic energy equivalent task; RR, relative risk.

Source: Used with permission from Dempsey et al.[37]

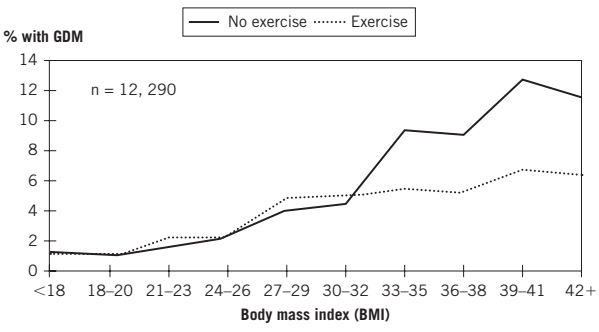

FIGURE 17-3 Prevalence of GDM by BMI and physical activity status 1995 to 1996 (central New York). (Used with permission from Dye et al.[41])

TABLE 17-3 Essentials for Laboratory and Home-Based Exercise Programs for Women With GDM

Laboratory-based program
- Three to four times/week, patient exercises at 50% VO2 max 45 min total, divided into three 15-min bouts with 5-min rests between each bout for a total of 45-min exercise.
- Fetus is monitored during 5-min rest periods.
- Plasma glucose and blood pressure are recorded before and immediately after each exercise session; maternal heart rate and uterine activity are monitored during and after exercise.
- Hemoglobin A1c is obtained at enrollment and then at 6- to 8-week intervals.

Home-based programs
- Patient is informed of potential complications.
- Patient rests for 30 min before breakfast, lunch, and dinner and monitors fetal activity.
- Patient monitors fasting and 2-h postprandial plasma glucose.
- If fetal activity and glucose levels are normal, she exercises for 20–30 min at 50% VO2 max (percent exertion fairly light to somewhat hard on a self-perception scale) after each prescribed meal.
- Patient rests for 30 min and counts fetal movements.
- If uterine contractions become regular or occur 15 min apart or less, patient notifies obstetrician.
- Patient keeps accurate records of blood glucose, food intake, physical activities, and fetal movements.
- Beginning at 32 weeks gestational, nonstress testing performed weekly; further fetal tests conducted as indicated.
- Hemoglobin A1c is obtained at enrollment and then at 6- to 8-week intervals.

Abbreviation: GDM, gestational diabetes mellitus.

may improve their long-term health and that of other members of their household.

Through indirect calorimetry, we established that carbohydrates are the preferential energy source utilized during 20–30 minutes exercise sessions.[25] From a physiologic standpoint, exercise is a logical therapeutic intervention for diabetes. As adjunctive therapy, it may avert or delay the need for pharmacologic intervention and limit the degree of that intervention if multifaceted therapy is required.

We recommend that exercise be initiated 30 minutes after a meal and continued for at least 20–30 minutes at 50% maximum aerobic capacity or higher at a self-perceived exertion of "moderate" to "somewhat difficult" (Table 17-3). Patients are advised to defer exercise and call or come in for evaluation if she is experiencing frequent uterine contractions, decreased fetal movement, or other concerning pregnancy-related symptoms, or her glucose level is persistently low or high (<80 mg/dL at 1 h post-prandial, >300 mg/dL). We instruct all patients to keep a food, activity, and glucose diary.[45]

SUMMARY AND CONCLUSIONS

GDM and type 2 diabetes have similar pathophysiology. Pregnancy and the postpartum period are ideal times for lifestyle modification. During pregnancy, women have easy and frequent access to medical supervision and care, more than any time in their life. Despite the easier access to medical care, women frequently mention barriers to exercise in pregnancy such as fatigue, nausea, edema, low back pain, and lack of time postpartum[46,47]; however, all reports indicate that higher levels of physical activity prior to pregnancy or in early pregnancy lower significantly the risk of developing GDM, particularly in overweight and obese pregnant women.

Lifestyle modification, exercise, and diet have been endorsed and advocated as a safe therapeutic adjunct in patients with GDM by ACOG, ADA, and ACSM. Women with previous GDM enrolled in the DPP to weight reduction and physical activity had a 53% reduction in type 2 diabetes, thus lifestyle modification, particularly exercise, is logical adjunct intervention to prevent or manage diabetes in pregnancy and beyond.

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The Genetic Architecture of Diabetes in Pregnancy

18

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Science is not like a puzzle; the picture we are assembling is changing while we are assembling it.

Key Points

- The genetic underpinnings of gestational diabetes mellitus (GDM) are complex, involving multiple genes that interact with the pregnant milieu and other factors.
- Genes that cause a relatively uncommon form of diabetes, autosomal dominant maturity-onset diabetes of the young (MODY), increase the risk for GDM.
- In addition, common variants that have a modest effect on risk for typical type 2 diabetes mellitus (T2DM) also appear to confer a modest increase in risk for GDM suggesting an overlapping genetic architecture between T2DM and GDM.
- Maternal and fetal genotypes interact to influence fetal birth weight.
- Insights into the genetic architecture of GDM may help to improve prevention and treatment of women with GDM and better maternal and fetal outcomes.

INTRODUCTION

Both type 1 diabetes mellitus (T1DM) and T2DM are multifactorial diseases caused by a combination of genetic and nongenetic risk factors. However, monogenic diabetes syndromes result from inheritance of single-gene mutations. Evidence also supports a genetic component to GDM with observations of concordance among siblings,[1] increased prevalence of diabetes mellitus in family members of those with GDM,[2,3] and increased risk for future T2DM in those with GDM.[4,5] With advancements in high-throughput DNA-sequencing methodology has come great progress in our knowledge of the human genome. Specifically, sequence variants in a number of genes associated with T2DM and monogenic diabetes have been discovered.[6] These breakthroughs have paved the way to begin to understand the genetic contribution to GDM although knowledge is lagging behind. Researchers have begun to investigate how genetic variants associated with T2DM and monogenic diabetes affect predisposition to GDM, and whether distinct variants in these or other genes influence GDM risk.

Understanding the genetic basis of GDM has significant implications for the mother, fetus, and family members. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study and other studies demonstrated that maternal hyperglycemia (and even glucose levels within the normal range) is associated with adverse maternal, fetal, and neonatal outcomes.[7] By understanding the genetics of GDM, we can better ascertain who is at risk, leading to earlier diagnosis and treatment and hopefully less adverse pregnancy outcomes. In the case of GDM caused by genes known to cause monogenic diabetes syndromes, more targeted therapy may be tailored to the specific gene change. In this chapter, we provide an up-to-date review of the genetic architecture of GDM and how this relates to the genetics of T2DM and monogenic diabetes.

GENES CAUSING MONOGENIC DIABETES SYNDROMES AND THEIR RELATION TO GDM

Monogenic diabetes syndromes can be inherited in an autosomal dominant, autosomal recessive, or mitochondrial (maternal) fashion, or mutations can arise de novo. They are estimated to account for approximately 5% of all diabetes cases.[8] Most commonly they result from mutations in genes causing β-cell dysfunction or loss resulting in impaired insulin secretion.[9] Less commonly, monogenic diabetes syndromes are due to mutations in genes that cause insulin resistance.[10]

MODY is the most common monogenic diabetes syndrome, with inheritance in an autosomal dominant manner. Patients typically present with diabetes at a young age (<30 years); furthermore, they are not obese, continue to make insulin, lack T1DM-related autoantibodies, and have other family members with diabetes.[11,12] Currently, mutations in at least 13 different genes have been implicated in causing MODY (Table 18-1).[13–15] Most commonly MODY is due to a mutation in a transcription factor gene involved in insulin secretion and β-cell developmental pathways.[9] The most frequent transcription factor-MODY is MODY3, caused by mutations in *TCF1*, encoding the transcription factor hepatocyte nuclear factor1α (HNF1α). MODY2, the second most common form of MODY, is caused by mutations in the glucokinase (*GCK*) gene.[11] The enzyme GCK is expressed in pancreatic β-cells and catalyzes the transfer of phosphate from ATP to glucose to form glucose-6-phosphate eventually leading to glucose oxidation, generation of ATP, closure of the ATP-sensitive potassium channels, and release of insulin into the circulation.[16] Mutations in *GCK* result in reduced glucose-stimulated insulin release.[11,17]

Unfortunately, MODY is often inappropriately diagnosed as T1DM or T2DM due to overlapping features.[18] The SEARCH for Diabetes in Youth Study sequenced the most common three *MODY* genes in antibody-negative subjects diagnosed with diabetes before age 20 and revealed that 94% of individuals with MODY were improperly diagnosed, mostly with T1DM (36%) or T2DM (51%).[19] Since it is not uncommon for MODY to present in young adulthood, it would be expected that its diagnosis, when suspected, can frequently be made in pregnant patients screened for GDM. Diagnosis of MODY in patients with GDM can have important implications for treatment and prognosis and for family members. For example, patients with transcription factor-MODY subtypes such as MODY3 and MODY1 experience progressive hyperglycemia usually necessitating treatment to prevent diabetes-related complications. These patients are especially sensitive to the sulfonylurea class of antidiabetic agents.[20] Patients with GCK-MODY, on the other hand, experience stable and mildly elevated blood glucoses that most often do not progress or cause complications and therefore do not typically necessitate treatment.

GCK-MODY and GDM

More research has focused on the association between GDM and GCK-MODY than transcription factor-MODY. Those with GCK-MODY are at a higher risk for development of GDM.[21] In addition, it is often during pregnancy that women with GCK-MODY are first recognized as having hyperglycemia and are diagnosed with GDM.[22] Approximately 50% of women with GCK-MODY have gestational diabetes and the prevalence of *GCK* mutations among women presenting with GDM is approximately 5%.[23–26] Published prevalence rates have been higher or lower depending on the clinical criteria used to test for *GCK* mutations. Ellard et al. found *GCK* mutations in 80% of women with GDM who met four prespecified criteria: persistent fasting hyperglycemia outside pregnancy (5.5–8 mmol/L [99–144 mg/dL]), an increment less than 4.6 mmol/L (83 mg/dL) during a two-hour oral glucose tolerance test, insulin treatment during at least one pregnancy but subsequently controlled on diet, a history of T2DM, GDM, or fasting hyperglycemia of >5.5 mmol/L (>99 mg/dL) in a first-degree relative.[27]

Knowing that fetal insulin secretion is a key determinant in fetal growth, Hattersley and Tooke hypothesized that a *GCK* mutation in the fetus would result in impaired insulin secretion and fetal growth, whereas a *GCK* mutation in the mother would only result in hyperglycemia, fetal hyperinsulinemia, and increased fetal growth.[28] In fact, when birth weight was studied in the presence or absence of *GCK* mutations in the fetus and the mother, birth weight was 533 g lower ($P = .002$) in the presence of a fetal mutation and 601 g higher ($P = .001$) in the presence of a maternal mutation.[29] Amongst 21 sibling pairs discordant for the *GCK* mutation, the child with the mutation in 19 of the pairs had a lower birth weight, with a mean difference of 521 g ($P = .0002$). Interestingly, no difference in birth weight was seen when both mother and fetus had the *GCK* mutation compared to

TABLE 18-1 Subtypes of MODY[13–15]

MODY Subtype	Gene	Clinical Features
MODY1	*HNF4A*	Progressive, risk of diabetes-related complications, sensitive to sulfonylureas
MODY2	*GCK*	Mild, nonprogressive hyperglycemia, low complication risk, no treatment required
MODY3	*TCF1 (HNF1A)*	Most common, progressive, risk of diabetes-related complications, sensitive to sulfonylureas
MODY4	*IPF1 (PDX1)*	Very rare
MODY5	*TCF2 (HNF1B)*	Associated with renal disease (i.e., renal failure, renal cysts)
MODY6	*NEUROD1*	Very rare
MODY7	*KLF11*	Very rare
MODY8	*CEL*	Very rare; can cause exocrine pancreatic insufficiency
MODY9	*PAX4*	Very rare
MODY10	*INS*	Can also cause neonatal diabetes
MODY11	*BLK*	Very rare
MODY12	*ABCC8*	Can also cause neonatal diabetes; sensitive to sulfonylureas
MODY13	*KCNJ11*	Can also cause neonatal diabetes; sensitive to sulfonylureas

when neither were affected, despite significant maternal hyperglycemia and no treatment. Similar findings have been reported in other families.[30] These findings suggest that when mother and fetus are concordant for a *GCK* mutation, less aggressive blood glucose management during pregnancy should be considered. In summary, both maternal and fetal GCK-MODY genotypes can interact and affect birth weight.

Further support for a role of *GCK* variants in GDM comes from the HAPO study in which a common variant (rs1799884), which has been shown to have a modest effect on T2DM risk,[31] is also associated with increased fasting and oral glucose tolerance glucose levels in pregnant women.[32] This variant is in the regulatory region of *GCK* and likely affects expression levels of an otherwise normal glucokinase enzyme.

Transcription Factor-MODY and GDM

Although less studied, the relationship between transcription factor-MODY and GDM has also been examined. Weng et al. found that amongst a population of Swedish women with GDM, the prevalence of transcription factor-MODY was 6%, with women carrying mutations in *TCF1* and insulin promoter factor1 (*IPF1*), resulting in MODY3 and MODY4, respectively.[33] Mutations in *IPF1* have also been found in members of an Italian family with GDM.[34] Another study examined *GCK* and *TCF1* mutations in a Polish population with GDM and found the prevalence to be 2% and 0.8%, respectively.[35] Common variants in *GCK, TCF1*, and *HNF4A* have been found to be associated with a modest increase in risk for T2DM. Shaat et al. genotyped over 1800 Scandinavian women both with and without GDM for common T2DM susceptibility variants in *GCK*, *TCF1*, and *HNF4A* and found that variants in *GCK* and *TCF1* were associated with increased risk for GDM, whereas the rs2144908, rs2425637, and rs1885088 variants of *HNF4A* were not.[21] These variants in *HNF4A* have a relatively small effect on T2DM risk (odds ratio [OR] = 1.22–1.27), and thus, sample size may not have been adequate to show a modest or even moderate effect on GDM risk.

Similar to the research done with *GCK* mutations and birth weight, researchers have examined how transcription factor mutations may play a role. Pearson et al. found that newborns with *HNF4A* mutations had a median birth weight 790 g greater than nonmutation family members ($P < .001$), regardless of whether the mutation was inherited from the mother or the father.[36] Macrosomia (birth weight > 4000 g) was significantly more common in affected than unaffected newborns (56% vs. 13%, respectively, $P < .001$) as well as rates of transient neonatal hypoglycemia (15% vs. 0%, respectively, $P = .003$). The mechanism seems to be fetal hyperinsulinemia, supported by studies of mice with *Hnf4a* deletions demonstrating hyperinsulinemia in utero and hyperinsulinemic hypoglycemia at birth. Although these findings are unexpected given *HNF4A* mutations typically lead to a decrease in glucose-induced insulin secretion, the results have been replicated in several other families.[37,38] These findings suggest that it might be prudent to offer genetic testing for *HNF4A* mutations to those with a family history of diabetes, born with macrosomia, and transient neonatal hypoglycemia. Unlike those with *HNF4A* mutations, *TCF1* mutation carriers did not have increased birth weight or neonatal hypoglycemia.[36] These findings were confirmed in other families with *TCF1* mutations.[39]

Less common transcription factor mutations have also been studied in relationship to birth weight. Italian newborns with *IPF1* mutations born to mothers with a mutation had significantly lower birth weights than an unaffected Italian newborn population ($P = .017$).[34] On the other hand, there was no significant difference in birth weight when unaffected newborns were born to mothers with the mutation compared to an unaffected population ($P = .50$). Edghill et al. examined patients with neonatal diabetes for mutations in *TCF2*, which encodes HNF1B, implicated in MODY5, and found that intrauterine growth was significantly decreased in patients born to unaffected mothers with 69% being small for gestational age ($P = .006$).[40]

In summary, it appears that both maternal and fetal transcription factor mutations influence birth weight. At this point, findings point to mutation-specific changes but studies are quite limited in number and sample size, and larger population- and mechanism-based studies are needed to better understand this relationship.

SUSCEPTIBILITY ALLELES FOR T2DM AND THEIR RELATION TO GDM

T2DM is a complex disease for which both genes and environment affect predisposition. It is polygenic, meaning there are many susceptibility variants, each with a small effect on risk. The influence of genetic susceptibility can be modified by lifestyle factors so that engaging in healthy eating behaviors and regular physical activity can decrease the risk of diabetes even in people who have a high genetic burden.[41] The introduction of genome-wide association studies has allowed for substantial progress in understanding the genetics of T2DM. Currently, there are 70 T2DM susceptibility loci identified,[42] most affecting insulin secretion.[41,43,44] These variants are common in the population, each conferring a modest increase in risk (OR = 1.1–1.4). Together, they account for only ~10% of the genetic contribution to diabetes leaving most of the inherited risk still to be identified.

A common genetic foundation for T2DM and GDM is suggested by their clustering in families, higher risk for T2DM in those with GDM, and a similar pathophysiology of insulin resistance and impaired insulin secretion.[2,3,45,46] In addition to common T2DM susceptibility variants in some of the same genes that cause monogenic diabetes mentioned earlier, common variants in transcription factor 7-like 2 (*TCF7L2*) and peroxisome proliferator-activated receptor-gamma (*PPARG*) are among the most studied T2DM susceptibility genes that have also been studied in GDM.

Transcription Factor 7-like 2

Association between genetic variants (e.g., rs7903146) in *TCF7L2* and T2DM was first demonstrated in an Icelandic population and then replicated in several other cohorts.[41,47,48] Compared with noncarriers, heterozygotes and homozygotes with the at-risk alleles were found to have a relative risk of T2DM of 1.45 and 2.41, respectively.[47] These findings have been widely replicated in diverse populations. For example, Damcott et al. compared the genotype frequencies of rs7903146 in *TCF7L2* in Amish subjects with T2DM, impaired glucose tolerance (IGT), and normal glucose tolerance (NGT).[49] When the T2DM/IGT group was compared with

the NGT group, there was a strong association with rs7903146 (P = .008; OR = 1.57). The risk (C) allele is common in the population, for example, in Caucasians, approximately 35% and 10% are heterozygotes and homozygotes, respectively; the frequency is even higher in African-derived populations and much lower in Asian populations. *TCF7L2* is a transcription factor important for pancreatic islet development and islet function.[41,48,49] Consistent with its role in pancreatic islet function, subjects with the risk allele have decreased insulin secretion compared to noncarriers.

Studies have consistently shown this same variant in *TCF7L2* to also be associated with risk for GDM. Shaat et al. genotyped the *TCF7L2* rs7903146 variant in women with and without GDM and found that heterozygotes and homozygotes had a 1.56- and 2.05-fold increased risk for GDM, respectively, compared with noncarriers.[50] In a similar study of a Greek population, the risk associated with this variant in *TCF7L2* for GDM was 2.69- and 3.25-fold for heterozygotes and homozygotes, respectively, compared with the wild-type homozygotes.[51] Amongst women from the HAPO cohort, those who carried the *TCF7L2* rs7903146 variant had a higher risk of GDM (OR = 2.04, 95% confidence interval [CI] 1.38–3.00; P = .003).[32]

The effect of *TCF7L2* polymorphisms on birth weight has also been examined. Among the HAPO cohort,[7] there was an association between maternal genotype and higher offspring birth weight but not between fetal genotype and birth weight. Freathy et al. further studied this relationship in other populations and found that a fetal copy of the *TCF7L2* rs7903146 susceptibility allele was associated with an 18-g increase in birth weight (P = .001), whereas each maternal copy was associated with a 30-g increase in offspring birth weight ($P = 2.8 \times 10^{-5}$).[52] When fetal and maternal genotype effects were adjusted for one another, the effect was predominantly maternal driven with a maternal copy of the allele resulting in impaired insulin secretion, maternal hyperglycemia, fetal hyperinsulinemia, and therefore increased intrauterine growth. Others have found no association between *TCF7L2* fetal genotype and fetal and early postnatal birth weight.[53,54] Thus, the burden of evidence suggests a modest effect of maternal *TCF7L2* variant on birth weight. Larger and long-term studies will be necessary to further define the importance of *TCF7L2* genetics to fetal outcomes.

Peroxisome Proliferator-Activated Receptor-Gamma

A potential role for the nuclear receptor PPARG in T2DM was originally suggested given its involvement in adipocyte differentiation, insulin sensitivity, and as a target for the antidiabetic drug class thiazolidinediones.[55,56] Genetic variants in *PPARG* have also been associated with T2DM risk. The SNP rs1801282 encodes a missense mutation that predicts the substitution of proline to alanine at codon 12 of the PPARγ2 isoform (Pro12Ala). Homozygosity for the more common Pro12 allele, present in approximately 75% of Caucasians, is associated with an increased risk for T2DM compared to carriers of the Ala12 allele.[57] A meta-analysis of the association found a 1.25-fold increased diabetes risk (P = .002), corresponding to a population attributable risk of 25% for the Pro12 allele.[58] On the other hand, the Ala12 allele is associated with a reduction in T2DM risk relative to Pro12 homozygotes (OR = 0.86, 95% CI 0.81–0.90).[59] The Ala12 allele is associated with increased insulin sensitivity, presumably the mechanisms whereby it protects from T2DM.

The association between Pro12Ala *PPARG* and GDM has not been as straightforward. Several studies including that by Pappa et al. of a large Greek population found no significant association between the Pro12Ala polymorphism and GDM.[51,60] However, other studies have shown a significant association such as when Chon et al. studied 136 Korean pregnant women and found that those with a Pro12 homozygotes genotype exhibited a 78% higher risk of GDM than Ala12 carriers (P = .027).[61] Although the relationship between Pro12 *PPARG* and GDM is inconclusive, a more consistent association between the Ala12 allele and increased maternal weight during and before pregnancy has been shown.[62]

Other T2D Susceptibility Variants and GDM

Assuming that the effect size of any single T2D susceptibility variants is similarly small for risk for GDM (OR = 1.1–1.4), large sample sizes would be required to tease out statistically significant differences in allele frequencies between GDM cases and non-GDM controls. Thus, most studies of the role of T2D susceptibility genes in GDM are underpowered. Cho et al. found that Korean patients with GDM were significantly more likely than those without GDM to carry SNPs in the T2DM-associated genetic variants *CDKAL1*, *CDKN2A/2B*, *HHEX*, *IGF2BP2*, *SLC30A8*, and *TCF7L2* with the ORs for GDM not significantly different from those with T2DM.[63] Similarly, Lauenborg et al. found ORs greater than 1.0 for common T2DM susceptibility variants in *CDKAL1*, *CDKN2A/2B*, *HHEX*, *IGF2BP2*, *SLC30A8*, *TCF7L2*, *FTO*, *PPARG*, *TCF2*, and *KCNJ11* in Danish women with GDM compared to those with NGT.[64] Specifically the variants in *CDKAL1*, *TCF7L2*, and *TCF2* were significantly (P < .05) associated with risk for GDM. Allele summing analysis of the 11 variants revealed increased risk of GDM for carriers of multiple risk alleles on risk of GDM (OR = 1.18 per risk allele, $P = 3.2 \times 10^{-6}$) (Figure 18-1). Women carrying 15 or more risk

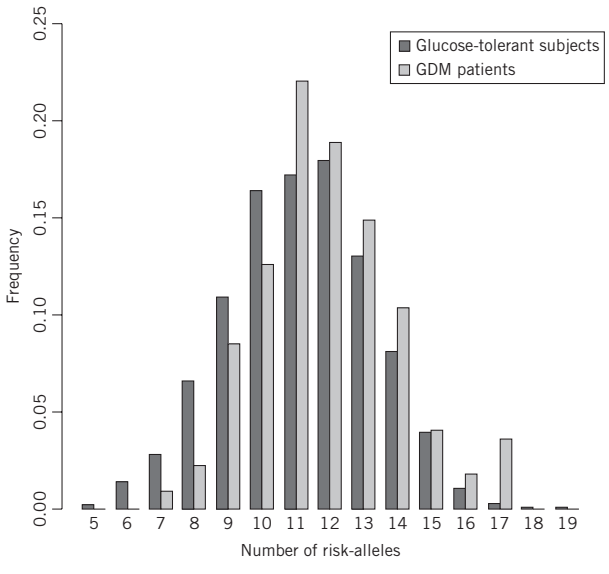

Figure 18-1 Subjects with GDM have a larger genetic burden of T2DM susceptibility alleles than normal glucose tolerant pregnant control subjects. (Adapted from Lauenborg et al.[64])

alleles had a 3.30-fold increased risk of GDM compared with women with 9 or fewer risk alleles ($P = 2.8 \times 10^{-4}$). Further corroborating these findings was a meta-analysis by Mao et al.[65] who examined 22 studies that included a total of 10,336 GDM cases and 17,445 controls. Common T2DM susceptibility variants in *CDKAL1*, *TCF7L2*, *IGF2BP2*, *MTNR1B*, *KCNJ11*, *KCNQ1*, and *GCK,* but not *PPARG*, were found to be significantly associated with GDM (Table 18-2). Although meta-analyses are prone to publication bias, prevailing evidence suggests that GDM and T2DM share similar genetic backgrounds.[66,67]

Novel Genes for GDM

To search for genetic variants for GDM distinct from known diabetes variants, Hayes et al. performed the first genome-wide association study of glycemia in 4437 28-week pregnant mothers enrolled in the HAPO study.[68] In addition to confirming associations with a number of known T2DM susceptibility gene variants, for example, *GCKR, G6PC2, PCSK1, PPP1R3B, MTNR1B, HNF1A, CDKAL1, YPS26A*, and *ARAP1*, two novel loci were identified. Rs4746822 in *HKDC1* was associated with two-hour plasma glucose levels ($P = 8.26 \times 10^{-13}$). *HKDC1* encodes hexokinase domain containing 1 for which little is known about its function. Second, rs6517656 in *BACE2* was associated with fasting C-peptide levels ($P = 3.06 \times 10^{-7}$). *BACE2* encodes beta-site amyloid beta A4 precursor protein cleaving enzyme 2, which may be involved in brain amyloid-beta deposition in disorders such as Alzheimer disease and Down syndrome. *BACE2* is expressed in pancreas, but its role in pancreatic amyloid deposition and islet

TABLE 18-2 Meta Analysis of T2DM Susceptibility Alleles in GDM

					Risk Allele			Dominant Model		
Variants per Gene	Risk Allele	Total/ Subgroup	No. Data Sets	No. of Case/ Control	OR (95% CI)	P(Z)	P(Q)	OR (95% CI)	P(Z)	P(Q)
PPARG Rs1801282	C	Total	11	2908/6940	1.01 (0.96–1.06)	0.80	1.00	1.14 (0.68–1.91)	0.63	0.45
		Caucasian	5	1559/5721	1.00 (0.94–1.06)	0.98	0.99	1.01 (0.58–1.76)	0.98	0.44
		East Asian	4	1149/1035	1.02 (0.93–1.11)	0.70	0.99	2.43 (0.38–15.43)	0.35	0.27
TCF7L2 Rs7903146	T	Total	6	3148/6550	1.51 (1.39–1.65)	<10–5	0.77	1.69 (1.51–1.89)	<10–5	0.51
		Caucasian	4	1812/4681	1.51 (1.38–1.65)	<10–5	0.48	1.71 (1.49–1.96)	<10–5	0.28
		East Asian	2	1336/1869	1.55 (1.16–2.09)	0.004	0.90	1.56 (1.24–2.22)	0.001	0.75
MTNR18 Rs10830963	G	Total	5	3094/4111	1.34 (1.18–1.52)	<10–5	0.02	1.46 (1.25–1.72)	<10–5	0.11
IGF2BP2 Rs4402960	T	Total	4	2304/5228	1.21 (1.08–1.36)	0.001	0.09	1.25 (1.07–1.49)	0.003	0.06
		East Asian	3	2030/2894	1.24 (1.07–1.44)	0.004	0.07	1.27 (1.12–1.43)	0.0002	0.81
KCNJ11 rs5219	T	Total	5	2305/5569	1.15 (1.06–1.24)	0.0004	0.99	1.25 (1.10–1.42)	0.001	0.88
		Caucasian	3	991/3698	1.17 (1.05–1.30)	0.005	0.98	1.25 (1.07–1.46)	0.006	0.72
		East Asian	2	1314/1871	1.13 (1.02–1.26)	0.03	0.93	1.11 (1.03–1.20)	0.02	0.29
CDKAL1 rs7754840	C	Total	4	2959/3675	1.43 (1.20–1.71)	<10–4	0.0003	1.51 (1.33–1.82)	<10–4	0.008
KCNQ1 rs2237892	C	Total	3	2285/2168	1.20 (1.09–1.31)	<10–4	0.70	1.42 (1.18–1.71)	0.0002	0.97
KCNQ1 rs2237895	C	Total	3	2286/2168	1.20 (1.09–1.31)	0.0001	0.75	1.31 (1.16–1.48)	<10–4	0.54
GCK rs4607517	A	Total	5	2135/4193	1.12 (1.02–1.23)	0.01	0.41	1.15 (1.01–1.30)	0.04	0.43

Source: Adapted from Mao et al.[65]

function is not known. Although replication will be required, these data suggest for the first time that the genetic architecture of glucose homeostasis in pregnancy may also have features distinct from T2DM and MODY.

CONCLUSIONS

Tremendous gains in our understanding of the genetic contribution to T2DM and monogenic diabetes have occurred in the last several years. Following this lead have been advances in our knowledge of the genetic foundation of GDM, although we are still in the early stages. Current evidence suggests that relatively uncommon, but large effect *MODY*-gene mutations increase risk for GDM. Given the high prevalence of GDM in subjects with autosomal dominant GCK-MODY, screening for mutations in *GCK* in patients with GDM and a family history of T2DM and/or GDM should be considered. In addition, common variants that have a modest effect on T2DM risk also appear to confer a modest increase in risk for GDM suggesting an overlapping genetic architecture between T2DM and GDM. Furthermore, maternal and fetal genotypes seem to interact to influence fetal birth weight. Some of the interactions are well defined, such as *GCK* mutations and fetal birth weight, but others need further characterization. These insights into the genetic architecture of GDM may help to improve prevention and treatment of women with GDM and better maternal and fetal outcomes. Ultimately larger studies are needed to better define these relationships. In addition, future studies must focus on the discovery of new alleles for GDM and deepening our understanding of underlying mechanisms and pathways they effect.

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Fetal Testing in Pregnancies Complicated by Diabetes Mellitus

Why, How, and for Whom?

19

Oded Langer, MD, PhD

In its approach toward the shadow of birth, every child has the right not to be stillborn but well born

—Hellman

Key Points

- All types of diabetes in pregnancy when not optimally managed are associated with increased perinatal mortality.
- The pathogenesis of intrauterine fetal death includes maternal hyperglycemia, fetal hyperinsulinemia, and the development of metabolic acidosis rather than fetal hypoxia.
- The vasculopathy accompanying some types of diabetes is associated with fetal growth restriction and hypoxia.
- Awaiting the ideal randomized clinical trial should not preclude fetal testing protocols based on current clinical wisdom and experience.
- Developmental delay in state behavior patterns and lung maturation characterize the infant of the diabetic mother.
- There are conflicting data on the effects of diabetes on fetal state behavior and maturation that need to be considered when fetal evaluation is performed.
- The primary approach in fetal testing in diabetes should be nonstress testing (NST) and fetal movements (FMs).
- The second line of defense should include the biophysical profile (BPP), amniotic fluid volume (AFV), Doppler studies, and level of glycemic control.
- The diagnosis-related group (i.e., hypertension) should always be addressed in the decision-making process for elective delivery in the presence of either abnormal or normal testing results.
- Fetal testing should be performed once weekly from the 26th to 28th week of gestation.

A 42-year-old woman with G_1P_0 type 2 diabetes (first diagnosed 7 years ago) came to the clinic for the first time at 7 weeks gestation. She had been treated for diabetes with metformin 500 mg bid; HbA1c upon admission was 6%. Routine prenatal care included a 24-hour urine collection for protein (177 mg) at 12 weeks gestation; amniocentesis at 17 weeks; and fetal echocardiogram and fetal anatomy scan normal at 19 weeks. All other routine prenatal care and diabetic exams (e.g., for retinopathy) were normal. Glycemic profile throughout pregnancy was within the targeted levels of glycemic control. Fetal biometric and surveillance testing throughout pregnancy is displayed in Tables 19-1 and 19-2. At 39 and 4 days of gestation, at a routine clinic visit, an estimated fetal weight of 4698 g was identified. BPP was 10/10, and the patient was transferred to labor and delivery for primary cesarean section due to fetal weight estimation. An hour later, no fetal heart tones were heard, and intrauterine fetal death was confirmed by ultrasound. An autopsy report revealed a normal fetus weighing 4658 g with no congenital anomalies but with organomegaly: fetal heart 168%; liver 178%; and brain 110% based on standard chart for fetal weight at autopsy. *What went wrong? What could have been done to alter the outcome?*

The aforementioned case is a clear demonstration of care provider frustration over unexplained fetal death after seemingly appropriate management of the pregnant diabetic patient. It has become axiomatic, even with scant data to support it, that patients with poor glycemic control and especially fetal macrosomia are associated with higher fetal death rates in the final weeks of pregnancy. However, in diabetic patients who have achieved targeted levels of glycemic control, fetal demise appears to be less common.[1] The accepted and "obvious" observations are unfortunately not always the case. For example, in diabetic women with vascular disease and preeclampsia, fetal

TABLE 19-1 Fetal Surveillance Testing

GA	EFW	Percentile	AFI	BPP
24 ± 6	918	67%		
29 ± 3	1757	75%	21	
31 ± 5	2171	74%	26	
33 ± 3	3085	>90%	27	
35 ± 3	3265	>90%	17	8/8
36 ± 3	—	—	16	10/10
37 ± 4	3660	>90%	15	8/10
38 ± 4	—	—	21	10/10
39 ± 4	4698	>95%	14	8/8

Abbreviation: BPP, biophysical profile; EFW, estimated fetal weight.

growth retardation and demise may develop as early as the late second trimester. Several studies reported an association in both gestational diabetes mellitus (GDM) and pre-existing diabetes with higher rates of intrauterine fetal demise and neonatal death.[2,3] Another explanation for the high rate of fetal death in pregnancies compromised by diabetes is the high rate of congenital anomalies. Although it has been demonstrated that the rate of anomalies can be decreased in patients who achieved targeted levels of glycemic control, the majority of studies report an incidence of 8% to 9%. This is a three- to fivefold increase in comparison with nondiabetic pregnancies (2%–3%). Certain system anomalies occur at a disproportionately higher rate. Cardiac anomalies and, in particular, ventricular septal defects and complex lesions such as transposition of the great vessels occur about 5 times more frequently, and central nervous system malformation, in particular, neural tube defects and holoprosencephaly occur about 10 times more frequently. The sacral agenesis/caudal dysplasia complex is reported to occur up to 400 times more commonly among fetuses of mothers with diabetes.[4–7]

Advances in ultrasound imaging have made it possible to identify major structural/functional anomalies with greater precision and at progressively earlier gestational ages. The detection of major and lethal anomalies in high-risk populations, including pregnancies complicated by diabetes, is now 86% or more.[8] After recognizing the importance of reaching the targeted levels of glycemic control prior to conception, what remains is the response to what causes the reported decreased rate of anomalies. Is it improved care? Or, is it the increased rate of elective abortion after early diagnosis using new detection technology in the first and second trimesters?

There is a broad spectrum of opinionated approaches for antenatal fetal surveillance and timing of delivery of diabetic pregnancies among obstetricians and maternal–fetal specialists.[9] This chapter is an overview of fetal testing of the infant of the diabetic mother. Because of the paucity of well-designed studies, many of the proposed approaches are based on expert and consensus opinion. The chapter will address physiological considerations, pathogenesis of fetal death in the neonate of the diabetic mother, and approaches for the prevention of fetal death.

PATHOGENESIS OF FETAL DEMISE

Although the mechanism of intrauterine fetal death in pregnancies compromised by diabetes remains unknown, there are several plausible explanations. Extramedullary hematopoesis is frequently observed in stillborn infants of diabetic mothers, an indication that chronic intrauterine hypoxia was the likely cause of death. Poor glycemic control will result in the stimulation of the fetal pancreas to increase secretion from the beta-cells (fetal hyperinsulinemia), which in turn stimulates hematopoiesis and fetal erythremia. Cordocentesis studies have demonstrated the association of maternal diabetes with erythremia in poorly controlled patients. There is a shift to the left in the maternal oxyhemoglobin affinity and, therefore, reduced red cell oxygen delivery at the tissue level.[10] Hyperglycemia results in increased fetal glycosylated hemoglobin; the hemoglobin variant shifts the oxygen dissociation curve to the left. Fetal hyperinsulinemia may increase fetal metabolic rate and oxygen requirements in the presence of several factors such as hyperglycemia, ketoacidosis, and vascular disease; these, in turn, reduce the uteroplacental blood flow and fetal oxygenation.

Alterations in fetal carbohydrate metabolism may also contribute to intrauterine asphyxia. The marked islet cell hyperplasia in the stillborn macrosomic infant of the diabetic mother has prompted investigation of the effects of both insulin and glucose excess on fetal oxygenation. Hyperglycemia, when accompanied by minimal degrees of hypoxemia, can result in lactic acidosis and fetal death in animal models.[11,12] Finally, another explanation for fetal demise is fetal hyperinsulinemia that may result in electrolyte imbalance of hypocalcemia and hypokalemia causing fatal cardiac arrhythmia.

Aerobic and anaerobic glycolysis are substrate driven (glucose) and may result in an increase in oxygen demand and tissue hypoxia. In the human fetus, hyperglycemia correlates directly with lactic acid concentration and inversely with pH and

oxygen partial pressure.[13] The chain of events of fetal hyperglycemia leading to hypoxemia that triggers the anaerobic glycolytic pathway and metabolic acidosis (lactic) is a potentially deadly combination.

Several animal studies demonstrated the association between fetal hyperglycemia/hyperinsulinemia, hypoxia, asphyxia, and fetal death. In twin fetal lambs that were induced to chronic fetal hypoxemia, it was demonstrated that the rate of development of acidemia was accelerated and the reversibility reduced in the lamb receiving glucose infusion when compared to the lamb receiving saline.[14]In the primate (*Macaca mulatta*), fetal insulin infusions resulted in metabolic acidemia, profound bradycardia, and acute fetal deterioration ending in death.[15]

In some species (e.g., sheep), fetal hypoglycemia, often profound, may occur either spontaneously or as an effect of maternal fasting[16] and is not associated with adverse fetal consequence. In the primate fetus, including humans, fetal hypoglycemia does not occur spontaneously but rather in the presence of profound maternal hypoglycemia or fetal hyperinsulinemia, either responsive (to hyperglycemia) or experimental. The primate fetus does not tolerate hypoglycemia and deterioration and death soon follow. As demonstrated in Table 19-2, even subjects in good glycemic control will be out of the targeted glucose range a significant amount of time. Furthermore, even in nondiabetic patients, the glycemic profile varies throughout the day and characteristically will be elevated in the evening and at night.[17–19] This fluctuation in glycemic profile may expose the fetus to surges of glucose that may cause intermittent hypoxia and fetal hyperinsulinemia. These fluctuations will be even wider in the poorly controlled woman with diabetes especially type 1 and type 2. It is likely that, in these cases, hypoglycemia is a cause of sudden fetal death.

RANDOMIZED TRIALS IN FETAL SURVEILLANCE: DO THE ENDS JUSTIFY THE MEANS?

Was a randomized study design used to justify a given management protocol? This is a recurring question today in the practice of obstetrics and has, in fact, become a knee-jerk reaction in academic forums. Instead, the questions that need to be asked are: *Is a randomized study always needed or justified given the research question? Is it ethical to perform a randomized trial after a given test or intervention has already become the standard of care?*

Close to 200,000 pregnancies compromised by diabetes occur in the United States annually. These women need the best reassurance for fetal well-being. For the woman with diabetes who has experienced a stillbirth, any strategy that could have prevented this mishap would have been worthwhile, however marginal its effect might have been on the overall rate of perinatal mortality. The actual benefit to be derived from such strategies and their overall cost/benefit ratio are issues that have yet to be studied. "The train has already left the station" decades ago when fetal biophysical testing was introduced and a randomized controlled study would have been a practical and ethical endeavor. Today, after decades of using these modalities, it would be unethical to deny the mother and infant well-established standardized fetal surveillance modalities. Needless to say are the legal implications of failure to test a fetus that is stillborn. Therefore, we are left with second rate options that are to evaluate the efficacy of large-scale epidemiological data or prospective assessment of a given protocol for fetal testing.

A randomized trial is rarely conducted in isolation. Patients usually have different prior risks for adverse outcome. Any test is generally interpreted in conjunction with these prior conditions. Therefore, it is often difficult to isolate the test results as indicative of a specific condition. Although this confounding effect can be partially overcome with the use of regression analysis technique that measures the net effect of a given variable (test), it is still not full proof. Disraeli is credited with saying: "There is a lie; there is a damn lie; and, there is a statistic."

In general, randomized trials require large sample sizes especially for research questions associated with relatively small prevalence such as stillbirth, neonatal death, shoulder dystocia, and so on. For example, to prove or disprove the effect of a specific strategy on the overall risk of perinatal

TABLE 19-2 Type 2: Glycemic Profile During Pregnancy

	HbA1C	MBG	Percent Reading					
			Premeal (%)		Postmeal (%)		Bedtime/Sleep (%)	
			Above	Below	Above	Below	Above	Below
7 wk	6%	—	—	—	—	—	—	—
14 wk	6%	127 ± 20	—	—	—	—	—	—
28–29 wk	—	88 ± 27	33	0	0	0	28	12
30–31 wk	—	97 ± 32	32	0	16	27	16	19
32–33 wk	4.9%	95 ± 40	33	10	17	22	29	10
34–35 wk	4.9%	88 ± 31	15	20	4	13	22	20
38–39 wk	—	84 ± 30	20	7	38	7	31	39

Abbreviation: MBG, mean blood glucose self-monitoring.

mortality in diabetes in pregnancy (8–10/1000), an intervention demonstrating a 50% reduction in that risk (to 5/1,000) would require randomization of 10,400 subjects (5200 in each arm), providing 80% power to detect a significant difference at an alpha error level of 0.05. Therefore, it is not surprising that the literature is almost devoid of any prospective studies examining strategies for antenatal fetal surveillance in diabetes in pregnancies. The large number of women required to test the hypothesis if fetal surveillance is of benefit in pre-existing and GDM suggests that the cost may far exceed any benefit in our current testing schemes. Nonetheless, women nowadays expect perfect outcomes from their pregnancies.

Theoretically, only a randomized trial could fairly determine the potential frequency of both stillbirth and hypoxic injury in offspring of diabetic women *without other risk factors* who do not undergo routine fetal surveillance tests during the third trimester. Unfortunately, the majority of diabetic patients have other risk factors such as obesity, hypertension, nephropathy, and so on. Furthermore, most of the diabetic patients are enrolled in surveillance programs and undergo fetal testing at least once/twice weekly. Moreover, trials of tests not only test the test but also any intervention that results from an abnormal test result. A physician's interpretation of a test will determine the intervention protocol he uses, and no two interpretations and protocols are necessarily the same. It is inconceivable that a sufficient number of trials from a big enough sample size will be performed to cover all the possible combinations of tests linked to all blends of plausible treatment options.

THE EFFECT OF MATERNAL DIABETES ON FETAL BEHAVIORAL CHARACTERISTICS

It is well recognized that the infant of the diabetic mother has delayed maturation of the central nervous system, lungs, and state behavior. In turn, one would expect that this delay would be reflected in varying fetal test results. These characteristics should be considered when fetal testing protocols are designed, thus avoiding unnecessary interventions based on false results. Mulder et al.[20] in 20 women with type 1 diabetes found a 1- to 2-week delay in the emergence of all normal FM patterns, particularly in women who had poor glycemic control in early pregnancy. Fetal breathing movements, however, were observed at an earlier age than in nondiabetic controls. During the third trimester, fetuses of mothers with diabetes have fewer FMs and FHR accelerations but more breathing movements compared to controls.[21–23] In pregnancies complicated by diabetes, Robertson and Dierker[24] attributed fluctuations in maternal glucose levels to the disruption in fetal activity during the third trimester. It should be noted that level of glycemia does not affect all behavioral states. In fact, FMs are not influenced by the level of glycemic control, whereas fetal breathing is stimulated and increased by glucose administration to the mother. Thus, the cause of FM on one hand and earlier appearance of FM on the other hand in the infant of the pregnant diabetic woman should be more complex than just fluctuations in glycemic level.[25–27] Some authors report increased fetal activity,[28–30] whereas others report decreased fetal activity[31,32] in the presence of maternal hyperglycemia.

Habituation in the fetus of his behavioral state was suggested in the past few decades. This was done by studying the response of the fetus to music, light, and other stimuli. With the increased popularity of the use of vibroacoustic stimulation during antepartum and intrapartum periods, it was found that a healthy fetus after several repeat stimulations will recognize and stop responding, whereas the "comatose" fetus will continually respond with jerky movements. Doherty and Hepper[33] studied habituation patterns in fetuses of diabetic mothers by performing repetitive vibroacoustic stimulation. These fetuses took longer to habituate compared to controls, demonstrating delayed maturation of the central nervous system.

Several studies have examined the effect of maternal diabetes on the FHR pattern. Tincello et al.[34] studied computerized fetal heart rate recordings in 26 women with type 1 diabetes throughout the third trimester. They found that these tracings demonstrated delay in fetal maturation compared to uncomplicated pregnancies. The results were reflected in a greater incidence of absent high variability, as well as differences in short-term variability, basal heart rate, accelerations, and frequency of FMs. Similar findings were reported by others.[35] Weiner et al.[36] compared FHR patterns in women with well-controlled GDM or pre-GDM and nondiabetic controls. They found that FHR variability and frequency of accelerations were significantly reduced in the diabetic pregnancies and increased at a lower rate during the third trimester compared to controls.

Comparable to the controversy that occurs regarding the effect of maternal hyperglycemia on FMs and fetal breathing, is the issue of fetal heart maturation. The use of fetal activity patterns based on fetal behavioral states, in conjunction with FHR assessment, may provide a window of opportunity to begin to institute fetal surveillance on a sound physiological foundation. Nijhuis et al.[37] first described the concept of fetal states. It was demonstrated that fetuses, like neonates and adults, have sleep/wake cycles with characteristic patterns of rapid eye movements, breathing movements, and gross body movements. The FHR demonstrates accelerations coinciding with gross body movements during the wake cycles. As mentioned earlier, hypoxic fetuses will demonstrate the absence of fetal activity patterns, no fetal heat rate acceleration, and redistribution of the blood supply. There is conflicting evidence if maternal ingestion of glucose can affect NST testing results. Zimmer et al.[38] found that administration of glucose to nondiabetic women at 37 to 40 weeks gestation was followed by a decrease in FHR reactivity. Holden et al.[39] also demonstrated that there was no increase in FHR acceleration following administration of glucose to the mother. In contrast, others have found increased reactivity,[40,41] increased mean FHR,[42] or no difference[43] after glucose ingestion.

The conflicting evidence in studies addressing fetal heart rate characteristics and maternal glycemia suffer from several drawbacks such as small sample sizes. The sleep activity cycle was not addressed in the majority of studies. Thus, it may be the change in the sleep activity cycle and not the administration of the glucose that increased/decreased FHR. In fact, a common practice in many centers is to encourage the patient to eat something in the presence of a nonreactive NST of 20 to 40 minutes duration rather than attempt to wake the baby (acoustic stimulation) or to continue to record FHR for 90 to 120 minutes.

Furthermore, a yet unanswered question is what will be the response of the fetus to chronic maternal glycemia throughout the day on an ambulatory basis.

Hypoglycemia does not appear to have an adverse effect on fetal biophysical measures. We reported in three type 1 diabetic women who were in hypoglycemic comas the disappearance of FM, fetal bradycardia, and absence of FHR acceleration. When the maternal glucose levels were slowly corrected, the fetal behavioral states were restored.[44] Reece et al.[45] performed insulin-induced hypoglycemic clamp studies in pregnant women with type 1 diabetes, lowering the blood glucose concentration to 45 mg/dL. During hypoglycemia, there was a nonsignificant increase in fetal limb and body movements and no changes in fetal breathing movements or FHR. However, the level of hypoglycemia in the study should be considered, at best, mild hypoglycemia in respect to the maternal condition. The fetus in these conditions can make an appropriate adaptation without further damage. Other authors reported that insulin-induced maternal hypoglycemia was associated with increased frequency and amplitude of FHR accelerations[46] and fetal activity.

Delayed lung maturation in the diabetic fetus has for decades been considered the result of the maternal disease. The mechanism of this delay is poorly understood. The maternal hyperglycemia and resultant fetal hyperinsulinemia were suggested as the cause for delayed lung maturation. In general, the timing of fetal pulmonary maturation is linked to the level of maternal glucose control in diabetic pregnancies. Adequate glucose control may lower the risk of fetal pulmonary immaturity to that of the nondiabetic population. Poorly controlled diabetic women are associated with delayed appearance of phosphatidylglycerol. However, after 37 weeks gestation, no significant neonatal pulmonary disease occurred.[47,48] It was reported in a case-controlled study that the delay in lung maturation is 1 to 1.5 weeks in diabetic pregnancies. This delay coincides with the delay reported for FMs.[49]

In summary, there are conflicting data on the effects of diabetes on fetal state behavior and maturation. These potential differences between diabetic and nondiabetic infants need to be considered when fetal evaluation is performed and decisions for delivery are being made to prevent unnecessary iatrogenic damage.

ANTEPARTUM FETAL SURVEILLANCE: WHAT AND HOW TO TEST

Not long ago, the obstetrician's main objective was to monitor that the woman was carrying a live fetus and that she be able to distinguish FM. The typical question would have been: "Is your baby moving?" And "Let's listen to his/her heart," as he/she applied the fetoscope. Today, with the development of biophysical testing (ultrasound, FHR monitoring, Doppler studies), a window into the uterus has been opened for obstetrician observation of fetal intrauterine life.

Tests of fetal condition are applied during the second and third trimesters, the period of greatest risk of fetal demise. The goals of antepartum fetal surveillance programs are to eliminate intrauterine death, to detect as early as possible fetal compromise and congenital anomalies and prevent unnecessary premature delivery. Although these techniques have not been subjected to randomized clinical trials, they have been incorporated into patient care protocols. Although programs vary in their use and timing of testing techniques, what remains uniform is a commitment to the use of fetal testing in pregnancies compromised by diabetes with an emphasis upon normalization of maternal glucose levels. The primary clinical value of current antepartum fetal monitoring tests is the low false-negative rate and their ability to reassure the clinician that the fetus with normal test results is unlikely to die in utero. Therefore, in a metabolically stable patient, such testing allows prolongation of pregnancy with continued fetal maturation.

Biochemical Methods

Historically, biochemical tests such as estriol and human placental lactogen (HPL) were used to evaluate fetal well-being; however, they remain historical references since they are no longer in use. The key and only essential biochemical marker of perinatal risk in diabetic pregnancies is the *maternal glucose concentration*. It may be argued that most of the dramatic reduction in perinatal morbidity and mortality among diabetic patients is a direct consequence of glucose monitoring and control. Self-monitoring blood glucose using reflectance meters coupled with intensified therapy now provides excellent control in the ambulatory outpatient setting.[50]

Prenatal testing options have grown in number and complexity over the years. Current options include maternal serum and ethnic-based carrier screening, ultrasound, and diagnostic testing; there are, in addition, evolving technologies in microarray and noninvasive prenatal testing. In 2007, the American College of Obstetricians and Gynecologists recommended that screening and diagnostic testing for aneuploidy be made available to all pregnant women, regardless of maternal age. Information discussed with patients should include detection and false-positive rates, advantages/disadvantages, and the associated limitations of each test. Although many health-care professionals are offering testing options, information presented to patients can vary based on provider experience, knowledge, personal bias, and length of clinical encounter.

First Trimester Testing

In the first trimester, the evaluation of the fetus of a diabetic mother should include a transvaginal ultrasound examination to rule out gross congenital abnormalities and crown-rump length (CRL) measurements for dating. A complementary abdominal ultrasound examination for congenital malformations needs to be performed at approximately 20 to 23 weeks gestation. Abdominal circumference (AC), fetal weight estimation, body composition, and cardiac evaluation (echocardiography) will enhance identification of the constitutionally large or small infant. During the third trimester, serial sonographic measurements need to be performed to assist in the selection of the treatment modality and the detection of deviant fetal growth.

Well-designed research protocols are needed to maximize efficacy and safety. At the same time, we need to be realistic. Instead of more research, we need to endorse *better* research. Ultrasound biometry in the detection of aberrant development of the fetus of the pregnancy affected by diabetes is a major triumph in medical technology. The weight prediction formulae targeted to take account of the different body habitus of the fetus in diabetic pregnancy are well established. However, there is still a need

to develop formulae with greater accuracy and predictability to minimize errors and unnecessary intervention.

Diabetic fetal macrosomia can be identified in the third trimester. In contrast, some authors have suggested that first trimester testing will identify fetuses that are small for gestational age (SGA). Traditionally, measurements of the CRL have been considered one of the most precise dating methods (±4–7 days) until the 12th week of gestation. After this date, measurement becomes less accurate because of variable degrees of fetal flexion. The CRL is obtained by measuring the long axis of the embryo.

Pedersen and Molsted-Pederson[51] studied 99 diabetic women. In 38 women, the embryos' CRLs were more than 6 days below the mean for gestation. Seven of these fetuses (27%) with "early growth restriction" were later diagnosed as being anomalous. However, the use of CRL for predicting fetal anomalies remains questionable since almost one in three nonanomalous embryos of women with diabetes had early growth restriction. In contrast, several studies demonstrated no association between CRL and fetal anomalies.[52,53] Therefore, although a fetus may be growing in an abnormal restricted environment that may lead to adult disease, there is no reproducible evidence indicating that an early growth delay is associated with malformed infants.

Second-Trimester Biometry

To date, there are numerous logarithmic formulae for estimating fetal weight, but there is a lack of uniformity and accuracy in measurement. Virtually all EFW formulae systematically overestimate birth weight. The imprecision of the formulae to account for fat deposits in fetuses and difficulties in measuring the AC of fetuses of diabetic mothers may provide another explanation for the inaccuracies in EFW. However, most formulae are better at predicting macrosomia than predictions based on gestational age alone. In infants of women with poorly controlled diabetes, there is a characteristic enlargement of the majority of the organs but not of the brain. Increased weight of insulin-sensitive tissues, including the liver, pancreas, heart, lungs, and adrenals, has been demonstrated in the infants of diabetic mothers (e.g., an increase in liver size of 179%). Based on this finding, it has been suggested that morphometry be used to measure fetal liver length.[54]

It was found that the increase in liver length was evident as early as the 18th week of gestation and became more marked with increased duration of pregnancy. Furthermore, individual liver length measures did not always remain constant when they were followed serially throughout pregnancy. This approach may provide an early fetal marker in addition to maternal markers (level of glycemia) for initiation of pharmacological therapy in the pregnancy affected by diabetes. Neonatal fat contributes approximately 12% to 14% of total birth weight; it accounts for about 50% of the variance. However, the amount of fetal fat in the subcutaneous locations used in anthropometric models may account for 40% to 80% of total fetal fat. A serial ultrasound assessment is more predictive than a single ultrasound examination for assessing fetal growth and health. Assessment of fetal growth and clinical decision making for management should not be viewed in isolation. Other methods that characterize the abnormal diabetic fetus are heart, body composition, and liver size—all of which assist in differentiating between the constitutionally and abnormally large fetus. In addition, clinical factors such as glycemic profile and obesity should be included in the overall assessment to maximize a successful delivery.[54]

Determination of fetal morphology can be made already in the second trimester with ultrasound technique. The initial scan between 16 and 18 weeks gestation yields accurate information (±7 days) regarding gestational age (if not obtained in the first trimester). At this age, morphometric screening for central nervous system and major gastrointestinal anomalies are reliable with cardiac and renal anomalies less easily diagnosed at this gestational age. With a suspicion of fetal anomaly, a second scan should be performed at 20 to 22 weeks. In addition to the general anatomic survey, there should also be a focused cardiac, facial, and limb scan at this time.

Biophysical Testing

NST is the most commonly used testing method, performed weekly or semiweekly from 26 to 28 weeks of gestation onward. Some authors have suggested that this testing method alone may not be optimal because the incidence of false-positive tests is high, ranging from 8% to 15%[55,56] and is increased in the premature fetus (≤30 weeks). The high false-positive rate can be decreased significantly by elongating testing time.[57] Furthermore, the European approach of interpreting NST into four categories of reactive, suspicious, nonreactive, and terminal/pathological will allow greater flexibility in the assessment of these patients.[58] Most groups that use the NST rely on the BPP score for additional information when needed. Others use the BPP as the primary assessment tool for the fetus.

Contraction stress test (CST) remains a valuable test in the evaluation of the diabetic fetus. However, with the recognition of the BPP, it has become less popular.

Fetal BPP score is used as a backup test, particularly in very preterm gestation. BPP is a dynamic ultrasound-based assessment of a composite of acute (fetal breathing, movement, tone, heart rate reactivity) and chronic (AFV) indices of fetal health.[59–61] An association was shown between fetal BPP and fetal acidemia in the high-risk population ($r = 0.52$; $P < .001$).

AFV: Although historically polyhydramnios has been associated with diabetes, this is in part due to the increased rate of anomalies in pre-existing diabetes or as a result of poor control that is sufficient to cause osmolar reaction and increased urination in the fetus. In GDM, polyhydramnios is not a common finding and if it occurs will most likely be detected in an undiagnosed type 2 diabetic woman.

Asphyxia-related oligohydramnios occurs as a result of reflex redistribution of cardiac output yielding relative renal hypoperfusion. Currently, there is no data to suggest that this reflex and its renal consequence are altered in any way in the fetus of the diabetic mother. As in nondiabetic mothers who have additional complications (e.g., SGA, hypertension), oligohydramnios may be a predictor of chronic asphyxia. In nondiabetic mothers, with isolated oligohydramnios, one can expect a nonasphyxiated fetus. However, diabetes alone is a complication, and therefore, the combination of diabetes and oligohydramnios should be considered abnormal.

Fetal Doppler Velocimetry

A 27-year-old primigravid, insulin-dependent diabetic woman, white class B, was found to have a high-resistance index on routine

Doppler screening at 23 weeks. Her glycosylated hemoglobin was elevated throughout pregnancy (mean 13%, range 9.4%–17.2%). At 29 weeks gestation, studies showed no end diastolic flow in the umbilical artery. Cordocentesis revealed oxygen tension of 3.4 kPa and pH 7.35. At 32 weeks gestation, because of fetal heart rate deceleration on the NST, patient was delivered by cesarean section. A female infant weighing 1660 g with cord blood pH of 7.20 was delivered.

This represents a case of who comes first: the biophysical or the Doppler velocimetry abnormalities? What is the impact of glycemia in these cases?[62]

A maternal factor that may play a role in the control of fetal growth is uteroplacental blood flow. If nutrients and oxygen cannot be delivered in adequate amounts to the fetus, fetal growth may be restricted.[63] With the aid of the Doppler technique, we[64,65] demonstrated a relationship between maternal diabetes, glycemic profile, and alterations in fetal blood flow to the placenta as measured by umbilical vein flow rates. When controlled for gestational age and estimated fetal weight, fetal–placental blood flow was 20% to 25% greater in diabetic women. In circumstances of either long-term maternal hypo- or hyperglycemia, fetal–placental blood flow was reduced and placental resistance increased when compared with euglycemic control. These changes in flow correlated only with the overall maternal glycemic profile and did not appear to be affected by acute changes in maternal glucose levels, consistent with a mechanism of chronic structural changes rather than acute vasoreactive changes in the placenta.

There is controversy over the role of Doppler waveform analysis in pregnancies complicated by diabetes. Studies in pregnant ewes demonstrated that chronic fetal hyperglycemia is associated with a 30% increase in fetal oxygen consumption[66] and acute maternal hypoglycemia produces redistribution of fetal blood flow to vital organs.[67] Moreover, in pregnant ewes rendered diabetic by streptozocin, fetal brain and renal perfusion increased significantly without any change in umbilical–placental blood flow.[68] These observations suggest that in the presence of maternal diabetes, placental perfusion does not change to meet the increased oxygen demands of the fetus, and Doppler waveforms of the umbilical arteries remain unchanged in the face of fetal hypoxia. Salvesen et al.[12] confirmed these findings in human pregnancies complicated by diabetes. Doppler studies of umbilical and fetal vessels were essentially normal except in the few cases complicated by preeclampsia or fetal growth restriction, whereas umbilical venous pH values were significantly lower than normal.

The association of abnormal Doppler indices with vasculopathy, hypertension, and fetal growth restriction in diabetic pregnancies has been demonstrated by several investigators.[69–72] Others[73,74] observed that in normotensive pregnant women with insulin-dependent diabetes, 34% had abnormal Doppler studies with increased risk of perinatal complications. They also studied GDM patients and found that 13% had abnormal Doppler indices without fetal growth restriction or preeclampsia. Bracero et al.[75] reported that abnormal Doppler studies obtained within one week of delivery are more reliable predictors of adverse outcome compared to the NST or BPP. Thus, there is lack of agreement on whether abnormal indices of Doppler flow velocimetry are associated with diabetes, per se, or only with diabetes complicated by vascular disease. Most authors, however, agree that the sensitivity of Doppler studies in determining fetal compromise in pregnancies complicated by diabetes is low, ranging from 32% to 61%. Williams et al. in a randomized study that compared NST with umbilical Doppler velocimetry found an overall similar outcome. The women in the Doppler velocimetry group had twice the rate of induction and a lower cesarean section rate for nonreassuring fetal heart rate tracing. The data suggest but does not prove that Doppler surveillance will detect the fetus at risk earlier than NST.[76]

Whether the quality of glycemic control affects Doppler flow indices and perinatal outcome is also a matter of controversy. Although Bracero et al.[77] first reported a significant correlation between umbilical artery S/D ratios and mean maternal blood glucose concentrations, other investigators have not found evidence of such a correlation.[78] Also, in hypoglycemic clamp studies, where maternal blood glucose concentrations of pregnant women with type 1 diabetes were lowered to 40 to 45 mg/dL, very slight or inconsistent changes in umbilical artery Doppler indices were observed.[45,46] In summary, it appears that Doppler studies of the fetoplacental vasculature have a clinical value for pregnancies complicated by diabetes and vasculopathy (D, RF, hypertensive disorder, etc.) In nonvascular GDM and pre-existing diabetes, Doppler studies perform a limited role.

WHEN TO START TESTING

Lack of clarity and controversy surround the issue of when to initiate fetal surveillance testing. A simple response would be that every fetus has the right to life and, therefore, testing should commence once he/she is a viable fetus. On the other hand, issues such as risk/benefit and cost/benefit ratios cannot be ignored.

Along the Borders of Viability

Factors influencing survival are measured differently. Some include or ignore intrapartum death, gestational age used for definition of stillbirth ranging from 20 to 30 weeks gestation, congenital malformations, gestational age definition using nearest week or completed weeks, and period of survival that can include from discharge, 28 days of life, up to 1 to 2 years. As a rule of thumb, the survival as reported by the National Institute of Child Health (NICHD) is approximately 24% at 23 weeks; 59% at 24 weeks; and 75% at 25 weeks. Similar survival rates are obtained using weight categories with 100 g increments from 500 g. It should be noted that these survival rates are associated with relatively high morbidity for the child.

Who decides for the newborn, and on what basis, when the fetus has the right to be tested to identify potential life-threatening risk? Is it the parents, the physician or both?

Disputes between physicians and patients over medical care have tended toward resolution in both the courts and ethics committees with each of these bodies ultimately deciding that the informed, competent patient must be the final decision maker. Parents, too, have the authority to make medical decision for their children, but these decisions can be challenged if physicians do not believe they are medically reasonable. One bioethical issue, however, is as intractable today as it was 30 years ago, when it began to be publicly discussed: the extent of parental authority to refuse life-sustaining medical treatment for an extremely premature infant. Who decides for the newborn, and on what basis, when

there is conflict between the parents and the physician? There is virtually no change in either the substantive criteria to apply to the decision or the procedures to follow, and decision-making is even more complex with extremely preterm infants.[79]

WHEN TO BEGIN TESTING THE GDM PATIENT?

Current beliefs echoed in many review articles and clinical opinions *not based on facts* are that fetuses of gestational diabetic mothers are not at risk for fetal death. However, all the new data suggest the opposite. Current studies suggest over threefold higher mortality in women with GDM compared to non-GDM[80] and national US data demonstrates three- to sevenfold higher rates of mortality as fetal weight increases.[81]

Kjos et al.[82] evaluated whether antepartum fetal surveillance testing can predict fetal distress in labor. Of 1400 women, 13% of women with GDM were admitted for delivery as a result of nonreassuring testing. There were two cases of intrauterine fetal demise at 36 and 38 weeks, 1 week after reassuring testing in women who had missed their previous interval testing session. There were no stillbirths within four days of reassuring testing. They did not use antenatal testing prior to 40 weeks in women with uncomplicated GDM treated with diet alone and performed NST twice weekly from 34 weeks onward in women with complicated GDM and in all women treated with insulin. Like all nonrandomized studies, this study and others cannot provide the information of what would be the rate of stillbirths in the 13% of patients who were admitted for elective delivery. Girz et al.[83] reported 3 stillbirths within 72 hours of reassuring testing in 389 GDM pregnancies. Seven percent of women were delivered as a result of nonreassuring testing. Their clinical protocol for testing diabetic patients included weekly testing from 28 to 34 weeks and then biweekly until delivery. Johnson et al.[84] reported no stillbirths among 188 GDM pregnancies and a 2.7% delivery rate for nonreassuring testing. They are opponents of the BPP for antenatal fetal surveillance including GDM pregnancies. They recommend a BPP once a week from 32 weeks onward in women with diet-controlled GDM and twice weekly from 32 weeks for women treated with insulin.

Landon and Gabbe[85] recommended no antenatal testing before 40 weeks for patients with uncomplicated GDM treated with diet alone. For women with complicated GDM (chronic hypertension, history of previous stillbirth, preeclampsia, maternal complications), regardless of treatment modality (diet or insulin), they recommend monitoring FMs from 28 weeks and twice weekly NST from 32 weeks onward. These recommendations are based in part on a series of 261 women with GDM and normal fasting who were tested at 40 weeks.[86] In another study of 97 women treated with insulin, FMs were recorded daily and antepartum surveillance began at 40 weeks. However, complicated GDM testing was initiated on a weekly basis at 34 weeks.[87] Coustan described the fetal testing protocol at his institution. For diet-treated patients, testing is initiated at 40 weeks and includes twice weekly NST and amniotic fluid assessments. For insulin and complicated GDM, testing ensues at 36 weeks or before, depending on clinical evaluation.[88]

The Fourth International Workshop on GDM[89] in 1997 recommended that decisions regarding the commencement and frequency of fetal surveillance be influenced by the severity of maternal hyperglycemia and the presence of other adverse clinical factors. Patients should be taught to monitor FMs from 24 weeks gestation (threshold for viability). In addition, NST should be considered from 32 weeks in cases where hyperglycemia warrants insulin therapy and at or near term in those requiring only dietary management. The American College of Obstetrics and Gynecology[90] concluded: "There is insufficient evidence to determine the optimal antepartum testing regimen for women with relatively normal glucose level on dietary therapy." Fuentes and Chez[91] reviewed 7 studies with a total of 491 patients studying antenatal fetal surveillance. There were seven stillbirths in the studies, two of these associated with congenital malformations not compatible with life and three stillbirths in GDM mothers requiring insulin. They concluded that, overall, the sample sizes were too small to affirm or deny the value of antepartum fetal testing in well-controlled insulin-managed diabetic women.

The general principles behind these practices are based on the assumption that women with uncomplicated GDM who are controlled on diet alone are at very low risk for adverse fetal outcome; therefore, they do not require antenatal testing prior to 40 weeks gestation. Those who are treated with insulin incur a greater risk and, therefore, warrant antenatal testing starting at some point in the third trimester. There are, however, very few published data with few subjects to support this position.[50,92–95]

From a realistic perspective, only a small number of patients will be categorized as uncomplicated GDM with normal fasting plasma glucose managed with diet therapy. It has been demonstrated that even mild hyperglycemia (fasting < 95 mg/dL) is associated with adverse pregnancy outcome. In light of the fact that the majority of GDM patients is obese and older than non-GDM patients and carries the added burden of preeclampsia and chronic hypertension leaves few patients who will not need fetal testing from diagnosis. It is the ethical responsibility of the physician to treat and provide the best medical care to his/her patients in a timely manner. It is the author's opinion that in the presence of gestational and pre-existing diabetes, fetal testing should be initiated at viability, starting with FM count and NST on a weekly basis in addition to fetal growth monitoring and other tests as indicated. To start testing at 40 weeks gestation will expose some fetuses to higher risk of stillbirth. At the end, *every fetus has the right to be delivered well born and not stillborn*.

We found in a randomized study of insulin and glyburide therapies, comparable perinatal outcomes.[95] In another study, with intensified therapy that achieved targeted levels of glycemic control in the majority of patients, the stillbirth rate was 4–5/1000, comparable to the general population.[50] We evaluated perinatal mortality in 4757 GDM patients to 10,804 nondiabetic controls. The fetal surveillance protocol consisted of daily FM count and weekly NST as the primary mode with BPP and Doppler studies as the secondary mode for patients compromised by vascular disease. The stillbirth rate in the GDM group was 4.8/1000 in comparison to 4.2/1000 in the nondiabetic group. The neonatal death was 5.8/1000 for GDM and 5.3/1000 in the non-GDM women. Sixty-five percent of the GDM stillbirths were poorly controlled and 60% with growth diversity (large for gestational age/SGA). Fifty-two percent of the GDM stillbirths and 38% of the neonatal deaths were derived from the diet-treated group; 44% of stillbirths and 56% of neonatal deaths originated from the insulin group.[96]

If approximately 50% or more of the deaths occur in diet-treated GDM patients, it is mandatory that fetal testing be initiated at viability (approximately 28 weeks in reality) regardless of treatment modality.

In which pregnancy period do the majority of stillbirths occur? The answer to this question would again bring us closer to making a decision on when to start testing. Thirty-eight percent of the stillbirths and 57% of the neonatal deaths occurred after 37 weeks gestation. Moreover, 17% of the stillbirths and 14% of the neonatal deaths occurred between 24 and 30 weeks gestation (19-1, neonatal and stillbirth rates in GDM). These data again support the concept of timely fetal testing for both diet and pharmacologically-treated GDM women.

WHEN TO INITIATE FETAL TESTING IN PRE-EXISTING DIABETES

Less controversial and routinely accepted is the importance of antepartum fetal testing in pre-existing diabetes. Despite aggressive testing and development of newer technology in the past few decades, perinatal mortality has not markedly decreased.[5,7] The advent of self-monitoring blood glucose has facilitated the maintenance of glucose control. Overall, intervention for testing of abnormal fetuses is now performed in approximately 5% to 10% of pregnancies complicated by pre-existing diabetes.[85]

Drury et al. reported in a study of 129 insulin-dependent women that fetal surveillance was undertaken for only 19 women who also had additional pregnancy complications. Only one woman delivered because of the results of abnormal fetal heart testing.[96] However, the small sample size precludes making a determination whether only a subset of pre-existing diabetic women with pregnancy complications need to be tested or whether all pre-existing diabetic women should be enrolled in testing programs. In a study by Landon et al. of 114 type 1 diabetic women with overall mean blood glucose of 110 mg/dL during the first and second trimesters, 9% (10/114) of the study group required intervention for abnormal fetal testing.[56] Eight of these 10 women had either nephropathy or hypertensive disease. Nephropathy hypertension was associated with intervention for abnormal fetal testing in 9 of 20 women with these risk factors in comparison to 1 in 94 without these complications. Olofsson et al.[97] studied fetal testing from 1977 to 1984 using a weekly NST as the primary method. They concluded that the predictive value of normal NST is 99% to 100% regarding 5- and 10-minute Apgar scores and 95% regarding ominous intrapartum FHR patterns. Teramo et al.[58] studied 145 pregnant women with insulin-dependent diabetes. Nonstress fetal heart rate was used as the test to detect fetal distress. NST was performed every other day starting at week 32 of gestation and daily after week 34 until delivery. One hundred and eighteen (81.4%) had normal, 9 (6.2%) suspicious, and 18 (12.4%) pathologic FHR readings. Nine of the 25 women (35%) with poor metabolic control had a suspicious FHR recording, which was significantly more frequent than in women with good metabolic control (18 of 120, 15%). The mean value of HbA1C during the last trimester with pathologic FHR readings was 7.63%, which was significantly higher than in diabetic women with normal FHR (6.91%).

Lagrew et al.[98] sought to evaluate when testing should be started in all pregnancies that were managed in their centers from 1981 to 1991. The primary mode of surveillance was weekly contraction stress test with an interval mid-week NST. Patients with multiple equivocal CSTs or contraindication to stress testing were followed with twice weekly NST. Of six hundred and fourteen pregnancies complicated by insulin-dependent diabetes mellitus, 71% were class A/B; 14% class C; 10% D; and 5% FM. Forty-nine percent of the positive CSTs occurred prior to 34 weeks gestation with an intervention rate of 21%. Three stillbirths and 6 neonatal deaths occurred during the 10-year study period (perinatal mortality 14.65/1000). They concluded that pre-existing diabetic patients, especially class R or F, with additional pregnancy complications may require testing to be initiated at 26 weeks gestation.

We[99] recently evaluated our experience of perinatal mortality in pre-existing diabetes in a cohort of 1104 pregnancies (358 type 1; 746 type 2 diabetic women). The testing protocol was based on daily FM count and weekly NST as the primary mode. BPP was used as the secondary mode with the addition of Doppler studies for patients compromised by vascular disease. The overall stillbirth for type 1 and type 2 diabetes was 12/1000 and 13/1000, respectively, in comparison to 4.2/1000 in the nondiabetic population (sample size of over 10,000 women). The neonatal death for type 1 and type 2 diabetes was 8/1000 and 5/1000, respectively, in comparison to 5.3% in the general population. Over 60% of the stillbirths in type 1 occurred prior to 34 weeks, whereas approximately 70% in the type 2 occurred after week 37. In contrast, 90% of the neonatal death occurred after week 37. Finally, 73% of the stillbirths and 72% of the neonatal deaths occurred in LGA infants. Of interest, only 5% of stillbirths and 6% of neonatal deaths were growth-restricted fetuses (Figures 19-1 and 19-2).

The March 2005 American College of Obstetricians and Gynecologists Practical Bulletin, entitled Pre-gestational diabetes mellitus recommended: "…Antepartum fetal monitoring including fetal movements, counting, the non-stress test, the BPP and the contraction stress test when performed at appropriate intervals. … initiation of testing is appropriate for most patients at 32-34 weeks' gestation…However, testing at earlier gestational ages may be warranted in some pregnancies complicated by additional high risk conditions…twice weekly testing has been widely adapted."[100]

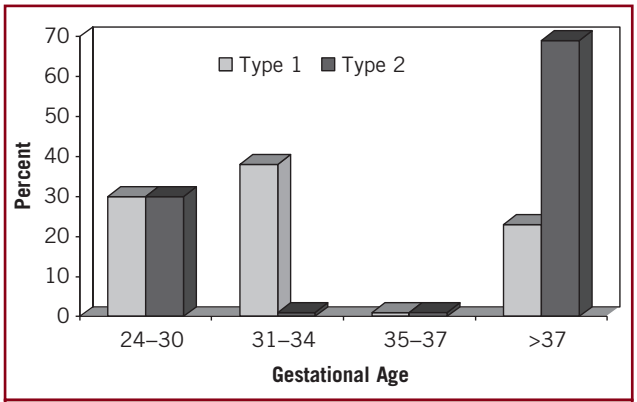

Figure 19-1 Stillbirth by gestational age.

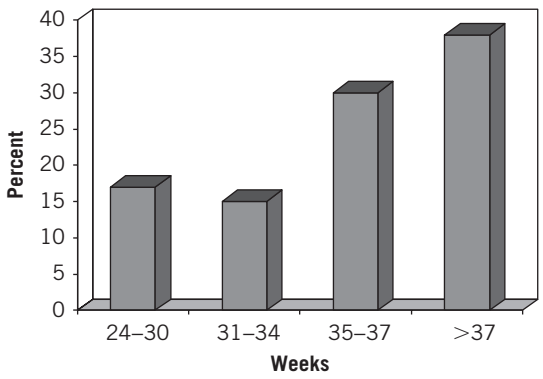

Figure 19-2 GDM: Stillbirth by gestational age.

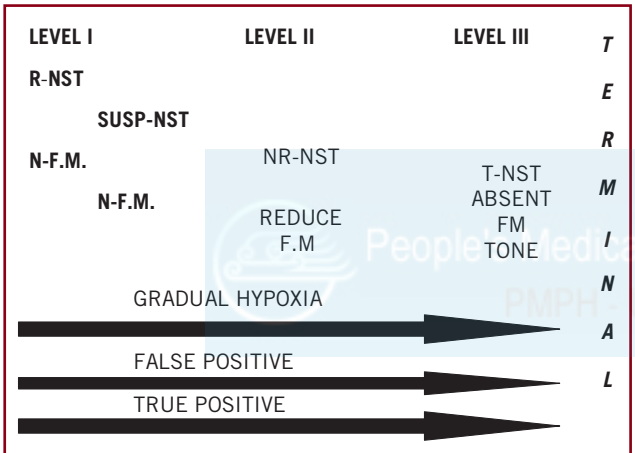

Figure 19-3 Testing categories preceding fetal injury.

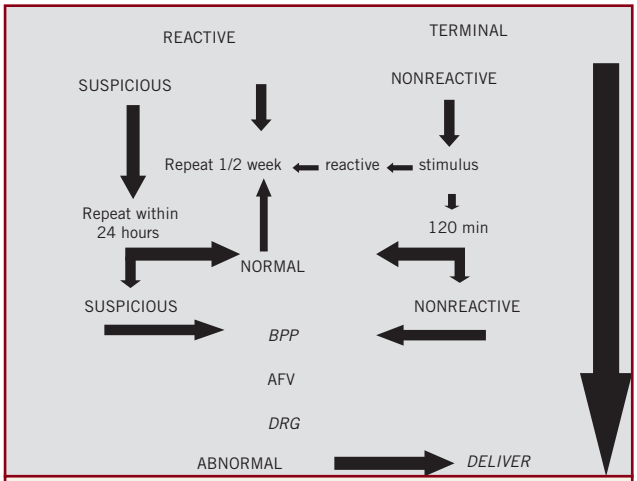

Figure 19-4 Decision tree for fetal assessment.

Our data and that of others[98] demonstrated that starting testing at 32 to 42 weeks will expose many diabetic fetuses to the risk of fetal death without major efforts to prevent it due to lack of testing. However, it leaves a segment of patients between 24 and 32 weeks gestation exposed to the risk of stillbirth without any attempt to prevent it. Again, it emphasizes the moral issue of the fetus versus the physician's opinion and cost considerations. Finally, weekly or twice-weekly testing remains the subject of opinions rather than data from even descriptive studies. Studies supporting twice-weekly testing are over 30 years old and the only additional data are sporadic case reports. It is the author's opinion, based on our program results, that testing should start at 26 to 28 weeks gestation (viability) and in the majority of cases weekly testing will be sufficient.

SUMMARY

The primary approach in fetal testing in diabetes in pregnancy can be the use of NST and FMs, and in the majority of cases, this combined testing approach will suffice to screen and identify the fetus at risk. Several barriers (levels) exist from normal testing to preterminal and/or fetal demise (Figure 19-3). As the second line of defense, testing should include the BPP, AFV, Doppler studies (especially for vasculopathy and growth restriction cases), and level of glycemic control. In addition, the diagnosis-related group such as hypertension should always be addressed in the decision-making process for elective delivery in the presence of either abnormal or normal testing results. Our experience using this approach once weekly from the 26th to 28th week of gestation resulted in perinatal outcome comparable to that in the general population including high-risk patients (Figure 19-4).

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Hypertensive Disorders in Pregnancy Complicated by Diabetes

20

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We cannot do everything at once, but we can do something at once.

—Calvin Coolidge, 30th US President

Key Points

- Hypertensive disorders are the most common medical complications of pregnancy (5%–10%) and a common cause of maternal mortality in the United States.
- The prevalence of diagnosed diabetes among adults in the United States has increased by 40% in 10 years, and more worryingly, it is estimated that this incidence will increase another 165% by 2050.
- Diabetes mellitus (including gestational diabetes mellitus [GDM] and pre-GDM) is equally common in pregnancy but often varies from 7% to 15% depending on the population studied.
- Patients with hypertension in pregnancy have a high incidence of eclampsia, abruptio placenta, preterm delivery (mainly iatrogenic preterm delivery due to obstetric intervention secondary to hypertension or its complications), disseminated intravascular coagulation (DIC), hemorrhage, renal insufficiency, pulmonary edema, stroke, and death. Perinatal morbidity and mortality are also increased from preterm delivery/prematurity and intrauterine growth retardation (IUGR).
- Preeclampsia complicates 9% to 60% of diabetic pregnancies; the rate increases as the severity of diabetes increases.
- New diagnostic and management criteria for preeclampsia and superimposed preeclampsia have been implemented per the Task Force statement.
- Hypertension and diabetes are systemic diseases with significant impact on the micro- and macrocirculation leading to nephropathy, retinopathy, cardiac disease, and so on; this underscores the need for aggressive control of blood pressure (BP).
- BP goals of <130 systolic and 80 diastolic in pre-GDM and hypertension. Normotensive BP ranges <140 systolic and <90 diastolic in the setting of left ventricular hypertrophy and renal disease.
- Calcium-channel blockers (CCB; diltiazem, nifedipine, etc.) are helpful in patients with chronic hypertension (CHTN) and diabetes because of their renoprotective effect.
- Angiotensin-converting enzyme (ACE) inhibitors may cause fetal renal insufficiency, oligohydramnios, growth restriction, cranial anomalies, and severe fetal hypotension especially in the second and third trimesters.
- Hyperinsulinemia could be the link between hypertension and diabetes mellitus. The presence of insulin resistance and hyperinsulinemia is associated with increased rates of atherosclerosis and cardiovascular complications.
- Preconception counseling is important to establish the etiology and severity of hypertension and diabetes and to identify end-organ damage and achieve adequate BP and blood glucose control prior to conception.
- Fetal programming leading to adult onset disease.

INTRODUCTION

Hypertension is the most frequent reason for office visits in the general population including male and female patients (pregnant and nonpregnant).[1] It is the most common medical complication of pregnancy being present in 5% to 10% of pregnancies.[2–5] The aforementioned figures may be grossly underestimated since the incidence of hypertension is said to have increased by about 40% to 50% in the past 10 years.[5,6] This increase is probably due to the alarming increase of obesity and the consequent increase in the incidence of diabetes mellitus in the United States.[6–8] Other possible reasons for the increase in hypertension in pregnancy include the increased rate of multiple gestation secondary to assisted reproductive technology and increase in age of pregnant women due to delay in having children.

Hypertension is the second most common cause of maternal death in the United States,[9] and African American women have a fourfold increase in mortality.[10] The mortality rate is also increased for women older than 35 years.[11] Patients with hypertension in pregnancy have higher incidence of eclampsia, abruptio placentae, preterm delivery (mainly iatrogenic preterm delivery due to obstetric intervention consequent to hypertension or its complications), DIC, hemorrhage, renal insufficiency, pulmonary edema, stroke, and death.[12] Perinatal morbidity and mortality are also increased as a result of preterm delivery/prematurity and IUGR (Table 20-1).

DEFINITIONS AND CLASSIFICATIONS

Hypertension is defined as a systolic BP ≥140 mm Hg or a diastolic BP ≥90 mm Hg. These measurements must be made on at least two occasions, no less than four hours and no more than a week apart. It is important to note that choosing the appropriate cuff size will help to eliminate inaccurate BP measurements. Abnormal proteinuria in pregnancy is defined as the excretion of ≥300 mg of protein in 24 hours or a protein/creatinine ratio of ≥0.30. The most accurate measurement of total urinary excretion of protein is with the use of a 24-hour urine collection. However, in certain instances, the use of semiquantitative dipstick analysis may be the only measurement available to assess urinary protein. Table 20-2 lists the classification of hypertension.

TABLE 20-1 Adverse Outcomes in Severe Hypertensive Disorders of Pregnancy

Maternal complications
- Abruptio placentae
- Disseminated intravascular coagulopathy
- Eclampsia
- Renal failure
- Liver hemorrhage or failure
- Intracerebral hemorrhage
- Hypertensive encephalopathy
- Pulmonary edema
- Death

Fetal–neonatal complications
- Severe intrauterine growth retardation
- Oligohydramnios
- Preterm delivery
- Hypoxia-acidosis
- Neurologic injury
- Death

Gestational Hypertension

Gestational hypertension is the elevation of BP during the second half of pregnancy or in the first 24 hours postpartum, without proteinuria, without abnormal blood tests (elevated liver enzymes, low platelets, or elevated serum creatinine), and without symptoms. Normalization of BP occurs in the postpartum period, usually within 10 days. Treatment is generally not warranted since most patients will have mild hypertension. Gestational hypertension in and of itself has little effect on maternal or perinatal morbidity or mortality when it develops at or beyond 37 weeks gestation. However, approximately 40% of patients diagnosed with preterm gestational hypertension will subsequently develop preeclampsia or severe features. In addition, these pregnancies may result in fetal growth restriction and placental abruption. Those with severe features in the setting of gestational hypertension are at risk for adverse maternal and perinatal outcomes and should be managed like patients with preeclampsia with severe features. If a woman with gestational hypertension receives antihypertensive therapy, she should be considered to have severe disease. Therefore, antihypertensive drugs should not be used during ambulatory management of these women.

Preeclampsia and Eclampsia

The classic definition of preeclampsia[15,16] with hypertension and proteinuria has been challenged and modified per the Task Force. Currently, meeting two criteria, hypertension in

TABLE 20-2 Classification of Hypertension

I. Gestational hypertension
- Systolic < 160 mm Hg or
- Diastolic < 110 mm Hg
- No proteinuria and no symptoms

II. Preeclampsia (hypertension ≥20 wk + proteinuria)
- Proteinuria definition: ≥300 mg/24 h or
- Protein/creatinine ratio ≥0.30 or
- ≥1 + on dipstick

III. Preeclampsia with severe features: any of the following
Severe Hypertension.
- Systolic ≥160 mm Hg or
- Diastolic ≥110 mm Hg
- Persistently severe cerebral symptoms
- Thrombocytopenia, 100,000/mm^3
- Elevated liver enzymes >2× upper limit normal
- Pulmonary edema
- Serum creatinine. 1.1 mg/ dL

IV. Chronic hypertension
- Hypertension before pregnancy
- Hypertension before 20 wk gestation

V. Superimposed preeclampsia
- Exacerbation of hypertension and/or
- New-onset proteinuria and/or
- Sudden increase in proteinuria

Changes have to be substantial and sustained.

VI. Superimposed preeclampsia with severe features: CHTN with any of criteria from III.

addition to proteinuria or symptoms, defines the syndrome of preeclampsia. Certain laboratory abnormalities are consistent with severe disease and are used interchangeably or in addition to symptoms.

Symptoms of preeclampsia include cerebral/visual symptoms, severe persistent right upper quadrant/epigastric pain unresponsive to treatment, and pulmonary edema. Laboratory abnormalities include thrombocytopenia with a platelet count <100,000, serum creatinine >1.1 mg/dL, and elevated liver enzymes (>2× normal).

Preeclampsia syndrome may be subdivided into preeclampsia and preeclampsia with severe features. The distinction between the two is based on the severity of hypertension as well as the involvement of other organ systems (Table 20-2). Close surveillance of patients with preeclampsia is warranted, as either type may progress to fulminant disease.

Risk factors for the development of preeclampsia include diabetes (particularly poorly controlled pre-GDM), obesity, nulliparity, extremes of age (more in teenagers and women with advanced maternal age [AMA], i.e., ≥35 years old), renal insufficiency or chronic renal disease, preexisting hypertension, personal history of preeclampsia, family history of preeclampsia, molar pregnancy, multifetal gestation, fetal hydrops, and thrombophilia.

HELLP Syndrome

A particularly severe form of preeclampsia is hemolysis elevated liver enzymes and low platelets (HELLP) syndrome (Table 20-3). The diagnosis may be deceptive because BP measurements may be only marginally elevated. A patient diagnosed with HELLP syndrome is automatically classified as having severe disease (Table 20-3).

Another severe form of preeclampsia is eclampsia, which is the occurrence of seizures not attributable to other causes.

Chronic Hypertension

Hypertension complicating pregnancy is considered chronic if a patient is diagnosed with hypertension before pregnancy, if hypertension is present prior to 20 weeks gestation, or if it persists longer than 6 months after delivery. The incidence of CHTN in pregnancy varies from 1% to 5%.[18,19] Essential or primary hypertension is the most common type of chronic hypertension contributing 90% of CHTN cases, while secondary hypertension accounts for 10%. Secondary causes of CHTN include renal diseases (glomerulonephritis, polycystic kidneys, renal artery stenosis), polyarteritis nodosa, lupus erythematosus, endocrine disorders (hyperaldosteronism, pheochromocytoma, diabetes mellitus especially with vascular involvement), and coarctation of the aorta.[14,20]

Women with chronic hypertension are at risk of developing superimposed preeclampsia. Superimposed preeclampsia is defined as an exacerbation of hypertension that was previously well controlled requiring escalation of BP medications and/or new onset of proteinuria or sudden increase in pre-existing proteinuria that has to be substantial and/or sustained.

Superimposed preeclampsia with severe features is defined by the presence of severe hypertension despite treatment, symptoms including cerebral/visual symptoms, persistent RUQ/epigastric pain unresponsive to treatment, or pulmonary edema. Lab abnormalities meeting criteria for severe features include low platelets <100,000 elevated liver enzymes (>2× upper normal) and serum creatinine >1.1 mg (new onset).

A research group recently proposed a prediction algorithm for CHTN patients with superimposed preeclampsia.[21] They performed a secondary analysis of 110 women enrolled in a trial of calcium supplementation for the prevention of preeclampsia of which 37 women had superimposed preeclampsia. They found that at 20 weeks gestation, women with systolic BP > 140 mm Hg, elevated uric acid (>3.6 mg/dL), and low plasma renin activity (<4 ng/mL) had a high probability of superimposed preeclampsia. The probability of superimposed preeclampsia was 86% if all three risk factors were present, 62% probability with two risk factors, and a reduction to 30% to 40% if only one risk factor was present. Further studies are required to help validate these results and ascertain their clinical efficacy.

TABLE 20-3 Laboratory Criteria for the Diagnosis of HELLP Syndrome[a]

Hemolysis
- Abnormal peripheral blood smear (burr cells, schistocytes)
- Elevated bilirubin ≥1.2mg/dL
- Low serum haptoglobin
- Significant drop in hemoglobin levels unrelated to blood loss

Elevated liver enzymes[b]
- Elevated ALT or AST ≥ twice upper limit of normal for the laboratory
- Increased LDH > twice the upper limit of normal for the laboratory

Low platelet count (<100,000/mm^3)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; LDH, lactate dehydrogenase; HELLP, hemolysis elevated liver enzymes and low platelets.

[a]Requires at least two of the abnormalities listed.
[b]Also elevated in severe hemolysis.

Diabetes Mellitus in Pregnancy

The incidence of diabetes mellitus in pregnancy (including GDM) varies from 7% to 15% of pregnancies in the United States.[18,22,23] GDM contributes about 90% and pre-GDM (type 1 and type 2) contributes 10% of the diabetic pregnant population.[17] GDM is due to carbohydrate intolerance that occurs during pregnancy secondary to metabolic changes especially in the third trimester. The maternal metabolic changes include increased production of progesterone, estrogen, human placental lactogen, free cortisol, prolactin, and glucagon. These agents have a diabetogenic effect on the mother.[24]

White's classification of diabetes in pregnancy included classes A, B, C, D, R, F, and H. The original classification was designed for pre-GDM; therefore, it did not include GDM (Table 20-4). There was no postrenal transplant group, understandably so, since in all likelihood, there were no pregnant renal transplant patients at the time. Modified White's classification is used in obstetrics because of the prognostic significance. The rate of perinatal mortality increases as the White classifications shift from class B to H.[25–27]

TABLE 20-4 Modified White's Classification of Diabetes in Pregnancy

Class	Age of Onset (y)	Duration (y)	Vascular Disease	Therapy
Class A				
GDMA 1	In pregnancy	In pregnancy	No	Diet controlled
GDMA 2	In pregnancy	In pregnancy	No	Insulin
Class B	>20	<10	No	Insulin
Class C	10–19	10–19	No	Insulin
Class D	<10	>20	Benign retinopathy	Insulin
Class F	Any	Any	Nephropathy	Insulin
Class R	Any	Any	Proliferative retinopathy	Insulin
Class H	Any	Any	Heart disease	Insulin
Class T	Any	Any	Postrenal transplant	Insulin

Hypertensive Disorders of Pregnancy Compromised by Diabetes

Preeclampsia–eclampsia syndrome complicates about 5% to 10% of all pregnancies. The incidence increases to 9% to 24% in women with pre-GDM without nephropathy (Table 20-5) and it is as high as 36% to 66% in women with diabetic nephropathy (Table 20-6).[28–37] The risk factors for preeclampsia in diabetic patients include nulliparity, pre-GDM, poor glycemic control early in pregnancy, pre-existing CHTN, microalbuminuria, and diabetic nephropathy. The rate of preeclampsia increases with the severity of the diabetes. A study by Yogev et al.[38] demonstrated a strong association between preeclampsia and the severity of GDM, whereas the study by Kvetny and Poulsen[39] showed a higher incidence of gestational HTN in GDM. Hanson and Person[33] found that poor glycemic control increased the risk for preeclampsia.

Hypertension and diabetes are systemic diseases with significant impact on the micro- and macrocirculation leading to nephropathy, retinopathy, cardiac disease, stroke, and so on. The damage to the end organs hinders correct diagnosis and monitoring of preeclampsia in patients with diabetes and CHTN.[40]

Diagnosis of preeclampsia in uncomplicated GDM is based on the standard definition of preeclampsia. A diabetic with CHTN but no proteinuria may be diagnosed with suspected superimposed preeclampsia if there is new onset proteinuria, worsening hypertension, or a sudden increase in preexisting proteinuria. Severe laboratory and/or clinical criteria change the diagnosis to superimposed preeclampsia with severe features and should be managed accordingly (Table 20-7).

Hyperglycemia and Hyperinsulinemia

The hypertensive effect of hyperinsulinemia is postulated to be due to weight gain, extra cellular fluid volume expansion due to renal sodium retention probably secondary to increased sympathetic activity due to insulin.[41] Hyperinsulinemia is suspected to be the link between hypertension and diabetes. They are intricately associated. When insulin resistance and hyperinsulinemia are present, there is an increased rate of atherosclerosis and cardiovascular complications.

Microalbuminuria and Diabetic Nephropathy

Microalbuminuria is one of four conditions associated with development and/or progression of diabetic nephropathy. The other conditions include pregnancy, poor glycemic control, and elevated BP.

Worsening renal function in a patient with pre-existing renal insufficiency may be due to preeclampsia but could also be secondary to worsening intrinsic renal function. Findings suggestive of preeclampsia rather than worsening renal function include increased levels of the aminotransferases, thrombocytopenia, and evidence of fetal compromise. Suggestive findings indicative of intrinsic renal pathology include the presence of red and white cell casts and/or cellular casts on urinalysis. Specific findings such as low complement levels in a patient with lupus erythematous may suggest intrinsic renal disease instead of preeclampsia. If the patient is remote from delivery and there is significant concern about misdiagnosis, then a renal biopsy is warranted.

MANAGEMENT OF HYPERTENSION IN PREGNANT DIABETIC PATIENTS

Preconception Counseling and Prenatal Evaluation

The pregestational diabetic woman should be evaluated at the initial prenatal visit to identify end-organ damage since such findings will change the patient's class (regardless of the duration of diabetes) and consequently the prognosis. According to Leguiman and Reece, about 30% of insulin dependent diabetes mellitus (IDDM) and 20% non-insulin dependent diabetes mellitus (NIDDM) patients have nephropathy and nearly two-thirds of the patients have proliferative retinopathy.[28] A study by Siddiqi et al. showed that almost one-third of pregnant women had benign or proliferative retinopathy early in the first trimester.[29] Therefore, preconception counseling is of utmost importance in the pregnant diabetic woman, more so, if complicated by hypertension. Initial evaluation includes 24-hour urine for total protein and creatinine clearance, renal panel or serum electrolytes, ophthalmoscopy or ophthalmology consult, electrocardiogram (EKG), and cardiology consult if there is an abnormal EKG (Table 20-8).

Ideally, preconception counseling and management should include establishing the etiology of hypertension, and identification

TABLE 20-5 Rate of Preeclampsia in Women With Type 1 Diabetes (Excluding Nephropathy)

Authors	Percent of Women	White's Classification	Preeclampsia	
			N	(%)
Garner et al.[31]	107	B, C	13	12.2
Greene et al.[32]	361	B–R	86	23.8[a]
Hanson and Persson[33]	463	B–R	53	11.5
Miodovnik et al.[34]	136	B–R	12	9.0
Kovilam et al.[35]	238	B–D	36	15
Sibai[30]	404	B–D	71	17.3
Total	1709		271	15.9

[a]Includes women with PIH.
Source: Courtesy of Sibai.[30]

TABLE 20-6 Rate of Preeclampsia in Women With Diabetic Nephropathy

Authors	No. of Women	Preeclampsia	
		N	(%)
Hanson and Persson[33]	31	18	58
Greene et al.[32]	59	39	66
Reece et al.[36]	31	11	35
Gordon et al.[37]	45	24	53
Miodovnik et al.[34]	46	30	65
Kovilam et al.[35]	73[a]	32	44
Sibai[30]	48	17	36
Total	333	171	51

[a]Includes women with White's classification R and F.
Source: Courtesy of Sibai.[30]

TABLE 20-7 Criteria for the Diagnosis of Suspected Superimposed Preeclampsia or Superimposed Preeclampsia With Severe Features

Suspected superimposed preeclampsia
- Exacerbation of hypertension that was previously well-controlled requiring escalation of blood pressure medications
- New onset of proteinuria
- Sudden increase in pre-existing proteinuria (substantial and/or sustained)

Superimposed preeclampsia with severe features
- Severe hypertension despite treatment
- Cerebral or visual disturbances
- Epigastric pain/right upper quadrant pain
- Pulmonary edema
- Abnormal liver function tests: Aspartate transaminase (AST) or alanine transaminase (ALT) >2 times the upper limit for the laboratory
- Thrombocytopenia (platelet count <100,000/mm^3)
- Serum creatinine >1.1mg (new onset)

TABLE 20-8 Diabetic Pregnancy Chart

Name:				
Date of birth:	G …P…		LMP: …/…/…	EDC: …/…/…
Type of diabetes:	I:	II:	Gestational:	Modified White's classification: A1, A2, B, C, D, F, R, H, T
HbA1c:	Date….. @ …..wk gestation		Date….. @ …..wk gestation	Date….. @ …..wk gestation
Triple screen at ……wk gestation (16–20 wk):				
Ultrasound:				
• First-trimester U/S (for correct dating and nuchal translucence [NT] measurement):				
• Fetal biometry/anatomy U/S (@ 18–20 wk):				
• Fetal Echo @ 20–22 wk gestation:				
• Follow-up growth U/S @ 4-weekly intervals				
Antepartum care:				
• Fetal kick count starting @ 28 wk gestation.				
Fetal testing @ 32 wk or sooner (for patients on insulin therapy):				
• Twice-weekly testing or BPP.				
• NSTs if there is poor growth.				
• NSTs and Doppler studies if IUGR (<10%).				
Renal evaluation: 24-h urine protein and creatinine clearance, electrolytes, urea, and creatinine levels				
EKG: (cardiology consult if EKG is abnormal)				
Ophthalmology consult/evaluation:				
Nutrition: Diabetic teaching, diet and counseling.				
Glucose monitoring: fasting, (±preprandial), 1 or 2-h postprandial, diner time, bedtime.				
Insulin regimen: morning dose, lunch dose, diner/night dose, and bedtime dose.				
Comments/comorbid conditions:				

of any end-organ damage and adequate control of BP and blood glucose levels prior to conception. Assessment of renal function is very important in patients with hypertension especially if there is co-existing diabetes mellitus. Laboratory investigations include urinalysis, urine specific gravity, and urine culture and sensitivity studies, blood urea, and plasma protein, 24-hour urine collection for total protein loss and creatinine clearance. Most of these tests are covered by the diabetic evaluation chart (Table 20-8). If there is any suspicion of pheochromocytoma, then 24-hour urine collection for estimation of vanyl mandelic acid may be included. Evaluation for other causes of secondary hypertension will depend on clinical suspicion or presence of risk factors for the secondary causes. The presence of proteinuria and the rate of increase of proteinuria may predict future deterioration of renal function in diabetic patients. Rate of decline of renal function is also affected by level of BP control. Renal function is more likely to decline in African American patients and those with AMA or pre-existing renal disease.[42]

Selection of Antihypertensive Agents for Pregnant Diabetic Patients

Tight BP control reduces progression of diabetic nephropathy and retinopathy in addition to reducing other cardiovascular problems in nonpregnant patients.[14,26,29–31] Tight BP control is encouraged in the preconception period, but during pregnancy, the rules change and tight control may cause uteroplacental insufficiency leading to reduced blood flow to the fetus.[43–45]

Maintenance of systolic BP below 160 mm Hg or diastolic BP below 110 mm Hg in a pregnant woman is the therapeutic goal for uncomplicated preeclampsia or mild chronic hypertension. In patients with diabetes, severe chronic hypertension, and/or evidence of end-organ damage, medical treatment should be initiated at systolic BP of 140 mm Hg or diastolic BP of 90 mm Hg[12] with an objective to maintain systolic BP ≤ 130, Diastolic BP ≤ 80. BP goals thus would be of <130 systolic and 80 diastolic in pre-GDM and hypertension. Normotensive BP ranges <140 systolic and <90 diastolic in the setting of left ventricular hypertrophy and renal disease. The therapeutic objective for treatment of severe hypertension is to prevent maternal cerebrovascular accidents and congestive heart failure without compromising cerebral perfusion or jeopardizing uteroplacental blood flow.

The treatment of hypertension in pregnancy may improve maternal outcome and possibly prolong pregnancy but it does not prevent preeclampsia or abruptio placentae, neither does it improve perinatal outcome.[46,47] The selection of antihypertensive agents in diabetic pregnant women is problematic. It is an attempt to reach a balance between saving the mother from the complications of uncontrolled or inadequately treated hypertension versus undue exposure of the fetus to potentially toxic or teratogenic medications.

TABLE 20-9 Antihypertensive Agents in Pregnant Diabetic Patients

Condition	Medication	Reason	Caution in Patients With:
Diabetes with normal renal function			
Pregnant	CCB	Renoprotective effect	• Renal insufficiency • Concurrent use of magnesium sulfate
Postpartum	ACE, ARB, CCB, diuretics	• Renoprotective effect	• Renal insufficiency • Avoid concurrent use of CCB and magnesium sulfate
DM with proteinuria only			
Pregnant	CCB	Renoprotective effect	
Postpartum	ACE inhibitors, ARB, CCB	Renoprotective effect	
DM with renal insufficiency			
Pregnant	CCB	Renoprotective effect	• Avoid ARB and ACE
Postpartum	ACE inhibitors, CCB	Renoprotective effect	• Avoid ARB • Avoid ACE if creatinine >3.0
DM and myocardial infarction	Beta blockers, ACE inhibitors, CCB	• Renoprotective effect • Improved cardiovascular outcome	
DM and heart failure	Diuretics, ACE inhibitors	Improved cardiovascular outcome	
DM and preoperative conditions	Beta blockers		May affect fetal heart rate if massive doses were given prior to cesarean section
DM and hyperthyroidism	Beta blockers		
DM and breastfeeding	Methyldopa, CCB (nifedipine)	• Extensively studied • Inexpensive	Abnormal liver function tests (LFTs) with methyldopa

Abbreviations: CCB, calcium-channel blocker; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; DM, diabetes mellitus.
Beta-blockers may increase hyperglycemia especially if used for prolonged periods.

A listing of maintenance antihypertensives that can be used during pregnancy (Table 20-9), as well as acute treatment of hypertension (Table 20-10), and magnesium sulfate dosage and potential side effects (Table 20-11) are provided in the following section.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

Angiotensinogen is converted to angiotensin I by rennin, and angiotensin I is converted to angiotensin II by ACE. Angiotensin II has two main receptor sites, type 1 and 2 receptor sites. The ACE inhibitors block conversion of angiotensin I to angiotensin II, while the angiotensin-receptor blockers (ARBs) block primarily the type 1 receptor sites. The type 1 receptors are highly expressed in the first trimester of pregnancy in the sheep placenta and may play a role in placental function.[48]

In the nonpregnant woman, ACE inhibitors (Lisinopril, Captopril) are the preferred agents for controlling hypertension in diabetic patients because of their renoprotective effect.[30] Unfortunately, ACE inhibitors may cause fetal renal insufficiency, oligohydramnios, growth restriction, cranial anomalies, and severe fetal hypotension especially in the second and third trimesters; therefore, they should be avoided in pregnancy.[27] Women on ACE inhibitors are advised to stop the medication prior to conception. However, if discovered in the first trimester, they may stop the medications without significant damage to the fetus.[49,50]

The use of ARBs (losartan, valsartan, irbesartan, candesartan) in pregnancy is still in the embryonic stage. They have similar indications as ACE inhibitors but are preferred in cases where the patient cannot tolerate ACE inhibitors because of cough.[51] The ARBs and ACE inhibitors can cause life-threatening angioedema and significant fetal toxicity. They may be used in the postpartum period in diabetic patients because of their renoprotective effect. It has been suggested that a combination of ARB and ACE inhibitors may be more efficient in reducing BP than either agent alone.[52] The recommendation is to avoid ARB if there is poor renal function since it may increase the potassium level.

The majority of investigators who have evaluated the influence of ACE inhibitors and ARBs on insulin sensitivity have agreed that there may be a slight increase in insulin sensitivity.

TABLE 20-10 Acute Treatment of Hypertension

Medication	Onset of Action (min)	Dose
Hydralazine	10–20	5–10 mg IV every 20 min up to maximum dose of 30 mg
Labetalol	10–15	20 mg IV, then 40–80 mg every 10 min up to maximum dose of 300 mg or continuous infusion at 1–2 mg/min
Nifedipine	5–10	10 mg po, repeated in 30 min, (20 mg po) × 2 doses, prn; then 10–20 mg every 4–6 h up to maximum dose 240 mg/24 h
Nicardipine		As continuous infusion at 3 mg/h with increments of 0.5 mg/h (titrated according to blood pressure)
Sodium nitroprusside	0.5–5	0.25–5 μg/kg/min IV infusion Risk of fetal cyanide poisoning with prolonged treatment.

TABLE 20-11 Magnesium Sulfate: Dosages, Serum Levels, and Associated Findings

Magnesium doses	
Loading dose	6 g IV over 20–30 min (6 g of 50% solution diluted in 150 mL D5W)
Maintenance dose	2–3 g IV per hour (40 g in 1 L D5LR at 50 mL/h)
Recurrent seizures	Reload with 2 g over 5–10 min, 1–2 times and/or 250 mg sodium amobarbital IV
Magnesium levels and associated findings	
Loss of patellar reflexes	8–12 mg/dL
Feeling of warmth, flushing, double vision	9–12 mg/dL
Somnolence	10–12 mg/dL
Slurred speech	10–12 mg/dL
Muscular paralysis	15–17 mg/dL
Respiratory difficulty	15–17 mg/dL
Cardiac arrest	20–35 mg/dL

The mechanism of action of ACE inhibitors and ARBs is not clear; however, it has been suggested that they improve blood flow and circulation to the skeletal muscles, facilitate insulin signaling at the cellular level, and enhance insulin and glucose delivery to tissues that improve insulin secretion by the pancreatic β-cells.

Calcium-Channel Blockers

CCBs (ifedipine, diltiazem, and verapamil) have a very good safety profile in pregnancy and have a renoprotective effect that may be useful in diabetic patients. A study by Sibai et al. evaluating the use of nifedipine in the management of preeclampsia demonstrated no obvious teratogenic effect.[53] Another study by Magee et al. at centers in the United States, Canada, and England evaluated 78 women with first-trimester exposure to calcium channel blockers. They followed the outcome of the pregnancies and compared them with that of a control group, which was matched for maternal age and smoking. They found no increase in major malformations in the study group compared with the control group and concluded that CCBs do not pose a major teratogenic risk.[54]

The short-acting form of nifedipine was used sublingually in the past for rapid reduction in BP but that route of delivery was discouraged because of complications; hence, the sublingual route is contraindicated. It is, however, still available in the oral form, both in short-acting and extended release. It may improve uteroplacental blood flow and has a tocolytic effect on the uterus. Nifedipine is used extensively in obstetric practice for both BP control and preterm labor without obvious teratogenic effects documented. Physicians are advised to exercise caution when using nifedipine in patients on magnesium sulfate since it may have a synergistic action leading to severe hypotension. This feature is even more evident in patients with renal insufficiency since it may affect the excretion of the drugs.

Verapamil is used for BP control in patients with cardiac disease. Further experience with Verapamil use in pregnancy is

available because of its use in treating arrhythmias in pregnancy; diltiazem may also be used in pregnant cardiac patients.

Alpha- and Beta-Blockers

Labetalol (alpha- and beta-blocking agent) is probably the most commonly used antihypertensive agent in pregnancy. It may be given orally or intravenously and, hence, may be used for routine BP control with easy conversion to parenteral route in case of severe hypertension, hypertensive crisis, or patients who are unable to take oral medications. The use of beta-blockers (atenolol, metoprolol, oxprenolol) in pregnancy has been studied and questions were raised about the possible teratogenic effects with atenolol. There have been reports of IUGR with the use of atenolol especially if taken in the first trimester but not later in pregnancy.[55]

Alpha-blockers are not used in pregnancy and may have limited role in the nonpregnant population since the recent publication of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. An arm of the study comparing doxazosin (alpha-blocker) and chlorthalidone (diuretic) in the treatment of hypertension was terminated because doxazosin doubled the risk of heart failure.[56]

Diuretics

Although preeclampsia and eclampsia patients may have edema and appear to be on fluid overload, they are very frequently intravascularly depleted. Consequently, most providers avoid diuretics in pregnant preeclampsia patients for fear of depleting the intravascular volume. Although that may be a concern in the intrapartum period, there is no reason not to use it in the postpartum period especially if there is pulmonary edema or evidence of fluid overload.

Following delivery, there is pooling of fluid from the periphery and the uterus into the circulation. This increases the intravascular fluid volume in which case administration of diuretics either as single agents or in combination with other antihypertensive agents is a reasonable route. One would expect an increase in the use of diuretics as antihypertensive agents now that studies have shown them to be as effective as, if not superior to, beta blockers.[57]

Thiazide diuretics and loop diuretics may be used in special circumstances especially in the postpartum period. Thiazide diuretics may cause hyperglycemia, thereby adversely affecting the control of hyperglycemia. However, this side effect is unlikely to have a large impact on outcome when diuretics are used for only a short period. The loop diuretics may cause hypokalemia; therefore, the serum level of potassium needs to be estimated if the woman is receiving the drug for more than a few days.

Central-Acting Agents

The central-acting agents include alpha-methyldopa (methyldopa) and clonidine. Until recently, methyldopa was the first-line agent for treatment of hypertension in pregnancy because it was probably the most studied antihypertensive medication with a well-documented safety profile. However, recent evidence indicates that it is no longer the drug of choice for BP control in both pregnant and nonpregnant patients. It has been shown not to be as efficacious as other readily available antihypertensive agents. In breast-feeding mothers with severe preeclampsia requiring medication, methyldopa may be used. Side effects of methyldopa include abnormal liver transaminases that might be difficult to differentiate from elevated liver enzymes due to preeclampsia.

Intrapartum, Postpartum, and Postoperative Care of the Hypertensive Diabetic Patient

Intrapartum magnesium sulfate ($MgSO_4$) should be administered to preeclamptic patients with severe features (for seizure prophylaxis) and eclamptic patients with the treatment continuing for at least 24 hours after delivery and/or 24 hours after an eclamptic seizure.[3,6,7,58] The dose needs to be adjusted in patients with renal insufficiency to avoid overdose due to poor renal clearance. Patients with CHTN do not need $MgSO_4$. However, all patients, including CHTN as well as gestational hypertension (GHTN), with severe features should receive $MgSO_4$. Such patients may have morbidity and mortality similar to that of preeclampsia with severe features patients. BP needs to be monitored for at least 48 hours in high-risk CHTN patients since they are more likely to have postpartum complications such as renal failure, pulmonary edema, and hypertensive encephalopathy.[3,11–14]

In the postpartum period, the appropriate antihypertensive agents (ACE inhibitors, ARB, CCB, diuretics, etc.) may be used without concern for teratogenicity. Although hyperglycemia may occur from the long-term use of beta-blockers and thiazide diuretics in diabetic patients,[59] they are safe for short-term use. Consider use of diuretics solely or in combination with other agents for treatment of HTN in the postpartum period, especially if treatment is required for a short period. These patients often receive large volumes of fluid as a result of prehydration prior to epidural anesthesia or intravenous fluid infusion with oxytocin (for induction or augmentation of labor) and magnesium sulfate (for seizure prophylaxis or preterm labor). Also, in the postpartum period, fluid is mobilized from the extra cellular space into the intravascular space, thereby increasing the intravascular volume. This scenario, often seen in women with severe preeclampsia and/or renal insufficiency, leads to increased risk for pulmonary edema and exacerbation of severe hypertension in the postpartum period.

Postpartum patients with fluid overload, massive generalized edema, or morbid obesity will benefit from the use of diuretic therapy alone or in combination with other antihypertensive agents. Loop diuretics such as furosemide are useful in patients with pulmonary edema or those that require a few days of antihypertensive medication. Thiazide diuretic-like chlorthalidone are preferred for patients with chronic hypertension who may require more than a few days of antihypertensive agents. Patients with cardiac disease, abnormal EKG, postmyocardial infarction, or congestive heart failure will benefit from the use of beta-blockers, CCB, ARB, ACE inhibitors, and diuretics depending on the comorbid condition in question.

Since preeclampsia with severe features or hypertension may develop in the postpartum period either as a new event or as an exacerbation of a mild form of the hypertensive disorder of pregnancy, all women should be educated about the signs and symptoms of severe hypertension or preeclampsia.

Prevention, Controversies, and Future Developments

Several randomized, placebo-controlled studies have evaluated the role of aspirin in the management of preeclampsia, but there is no conclusive evidence that it prevents preeclampsia.[40,60]

The Collaborative Low-dose Aspirin Study in Pregnancy trial (n = 9364 women) randomized subjects into either the placebo or the aspirin treatment arm. In the postpartum, 9309 women (99.4%) of the original study population were evaluated by chart review. The placebo-controlled group had 4650 women and aspirin-treated group had 4659 women. Most of the patients were randomized in mid-trimester with 62% entering the study before 20 weeks of gestation. About 6.7% of the aspirin-treated group developed proteinuric preeclampsia compared with 7.6% of the placebo group. Although this showed a reduction of 12% in the odds of developing proteinuric preeclampsia, it was not statistically significant. A study by Caritis et al. evaluated a subpopulation of primarily diabetic patients and still found no preventive role for aspirin in preeclampsia. The role of calcium, vitamin E, vitamin C, and other anti-oxidants is being studied; none of these has yet been recommended for prevention of preeclampsia.

McElvy et al.[61] evaluated the impact of adequate preconception care on perinatal mortality and congenital malformations in the management of pregnant women with type 1 diabetes. They reported a reduction in perinatal mortality from 7% to <1%, while the congenital malformation rate was reduced from 14% to 2.2%. They implemented strict preconception blood glucose control and regular fetal surveillance starting at 32 weeks gestation.

Racial differences in the incidence, mortality, and morbidity of diabetes and hypertension remain unsolved. Reasons for racial discrepancy in outcomes of diabetic and hypertensive management are still unclear. The intricacies, dynamics, and implications of the ALLHAT study especially as it affects ethnic groups is confusing.[62] To complicate matters, most studies are performed on nonpregnant patients, hence the need to encourage research on these medications for the pregnant population.

In a large observational study by Keenan et al., over 500,000 patients were included in the objective to examine the impact of chronic hypertension and pre-GDM on pregnancy outcomes.[63] The impact of chronic hypertension and pre-GDM was found to vary, with a finding of an additive effect in stillbirth, preterm birth, and delivery at 32 weeks.

Stella et al. have established that the coexistence of GHTN and GDM mellitus increases the risk of macrosomia, large-for-gestational-age infants, rate of cesarean delivery, and neonatal intensive care unit admissions as compared with individual groups with either GHTN or GDM alone.[64]

SUMMARY

An epidemic of diabetes is looming due to the growing number of children with obesity. The prevalence of diagnosed diabetes among adults in the United States has increased by 40% in 10 years and more worryingly, it is estimated that this incidence will increase another 165% by 2050.[65]

Sooner or later these adolescent diabetics will become pregnant and swell the already growing population of hypertensive, diabetic pregnant patients. These are at an increased risk for preeclampsia, one of the killer triad in pregnant women. Pregnancy complications also increase with preeclampsia in the setting of diabetes, and an additive effect was noted in pregestational DM as well as GDM and hypertension.[63,64]

Dr. David Barker's landmark studies, along with additional human and animal model data, had shed the lights on fetal origins of adult disease. In utero fetal programming can have implications not only on the fetus but also on the eggs in the case of a female fetus. Thus, high-risk exposures and conditions during pregnancy can directly contribute to poor health in the mother, as well as her kids and possibly grandkids.

Preventative intervention efforts should be established with a goal of optimizing women's health prior to, during, and postpartum. With the understanding of fetal programming, such an intervention would be key to optimize the health of unborn children.

All hypertensive and/or diabetic women within the reproductive age group who anticipate conception, therefore, are strongly recommended to have preconception counseling. Lifestyle changes are needed to try and improve BP and glucose control. Apparently, a weight gain of over 10 kg after 18 years of age carries increased mortality.[66] The relationship between body mass index, physical inactivity, and diabetes mellitus has been clearly established.[63] Obesity adversely affects blood glucose control, lipid levels, and BP.[67–69] In addition, diabetic women with a history of hypertension during pregnancy experience a higher cardiovascular mortality later in life.[63] The combination of chronic hypertension, diabetes mellitus, and smoking will increase the risk for abruption, IUGR, and long-term vascular complications, thus smoking cessation counseling is very important prior to pregnancy. All diabetic women contemplating pregnancy need to be counseled regarding the importance of prevention during the preconception period and require close medical attention during gestation and postpartum.

The increased understanding of the pathophysiology of hypertension in pregnancy, as well as advances in medical therapy so that risks of fetal toxicity and teratogenicity are minimized, will improve our ability to prevent and treat hypertension in pregnancy. It is clear that in diabetic women, complications of diabetes, particularly diabetic nephropathy and poor glycemic control, are independent risk factors for hypertension (Tables 20-5 and 20-6).

By understanding the relevance of the risks of the obesity/diabetes epidemic and its hypertensive complications, health-care professionals and policy makers need to make this issue a high health-care priority and implement preventive measures and treatment for those at higher risk for chronic diseases. If no such intervention would take place, I would only say…be afraid, be very afraid.

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PART III Pregnancy Complicated by Gestational Diabetes Mellitus

Pathogenesis of Gestational Diabetes Mellitus

21

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The world isn't just the way it is. It is how we understand it.…
And in understanding something, we bring something to it…

—Yann Martel (Life of Pi)

Key Points

- Normal Pregnancy is characterized by a 40%–50% decrease in peripheral (skeletal muscle) and endogenous (primarily liver) insulin sensitivity; as a result there is a two- to threefold increase in insulin secretion and insulin clearance by 20%–30%
- Gestational diabetes mellitus (GDM) is characterized by inadequate pancreatic β-cell response for the increased level of insulin resistance present in women with GDM as compared with a matched control group
- Women with GDM have approximately 50% less total insulin secretion in comparison to non-GDM women

INTRODUCTION

Gestational diabetes (GDM) is the most common type of diabetes identified during pregnancy, affecting 3%–7% of all pregnancies.[1–3] For any gravida, the natural increase in insulin resistance with subsequent increasing postprandial glucose levels, makes pregnancy a "diabetogenic state." In a pregnancy not complicated by GDM, the increase in insulin resistance is met by an increase in insulin production to maintain a euglycemic state.[4] In contrast, women who develop GDM can have a suboptimal insulin response (a failure of the pancreatic β-cell to compensate for the increasing insulin resistance), a decrease in peripheral and central insulin sensitivity, or a mix of both.[5] Although primarily a disorder of glucose metabolism, GDM affects all aspects of maternal nutrient metabolism. However, the basic pathophysiology of GDM can be established by describing the changes that lead to a deviation from the normal glucose homeostasis of pregnancy. This review will explore the metabolic imbalances that characterize GDM, both in terms of the insulin secretion/sensitivity relationship and disturbances in the rhythms of glucose homeostasis.

GLUCOSE HOMEOSTASIS/NORMAL PREGNANCY

Glucose homeostasis involves a complex relationship between blood glucose concentration (*G*), insulin response (*I*), peripheral insulin sensitivity (IS), hepatic glucose production (HGP), and insulin clearance (IC). Glucose is absorbed via sodium-dependent transporters on the apical membrane of the intestine against the normal concentration gradient. Subsequent efflux is facilitated by diffusion transporters on the basement membrane of the epithelium. Both the density of the transporters and the sodium gradient that drives the uptake regulate the transport of glucose. Within the fetal compartment, glucose concentration is a result of placental facilitated diffusion transporters solely and is then regulated by the concentration gradient and fetal metabolism.[6]

Facilitated-diffusion glucose transporters (GLUT) consist of several types that vary in their kinetic properties, functional roles and localization, with at least five subtypes important within pregnancy. GLUT1 is present in placenta, muscle, adipose tissue, brain, and endothelium and is involved in cellular metabolism. Present within the syncytiotrophoblast and on the microvillous and basal membranes, GLUT1s are the primary transporter of glucose to the fetus.[7] GLUT2 is present on pancreatic β-cells, liver, small intestine, and renal proximal tubules and acts as a glucose sensor and fructose transporter. GLUT3 is present in neural tissue and the small intestines and acts as a scavenger under conditions in which *G* is low and in high demand due to increased metabolism. GLUT4 is expressed only in insulin-responsive tissue such as muscle, heart, and adipose tissue. Finally, GLUT5 is a fructose transporter found in the small intestine, brain, muscle, and adipose tissue.[8,9]

Peripheral glucose metabolism primarily takes place within skeletal muscles requiring the GLUT4 transporter. Studies in human skeletal muscle and adipose tissue have demonstrated defects in the post-receptor insulin-signaling cascade during pregnancy. Friedman et al. showed that women in late pregnancy have reduced insulin receptor substrate-1 (IRS-1) concentrations compared with those of nonpregnant women.[10] Downregulation of the IRS-1 protein closely parallels insulin's decreased ability

to induce additional steps in the insulin-signaling cascade, which normally result in the transporter (GLUT-4) arriving at the cell surface to allow glucose to enter the cell. During late pregnancy in women with GDM, in addition to decreased IRS-1 concentrations, the insulin receptor-β (i.e., component of the insulin receptor within the cell rather than on the cell surface) has a decreased ability to undergo tyrosine phosphorylation.[10] This is an important step in the action of insulin after it has bound to the insulin receptor on the cell surface. This additional defect in the insulin-signaling cascade is not found in pregnant or nonpregnant women with normal glucose tolerance and results in a 25% lower glucose transport activity (Figure 21-1).

Once glucose is absorbed, insulin secretion increases to return the *G* to normal levels (Figure 21-1). It is apparent with a glucose load that *G* and *I* oscillate back and forth to achieve a homeostatic level. The time that glucose rises before returning to fasting levels reflects the homeostatic control of the insulin–glucose interaction, the responsiveness, and output of the pancreatic β-cells, and can distinguish normal from the abnormal responses typical of diabetes in and out of pregnancy.[11] The relationship between the amplitude and time taken for the oscillations to disappear (dampening time) is indicative of the efficiency of the control system and the insulin resistance of the tissues. In early pregnancy, maternal insulin requirements increase over the prepregnancy state (Figure 21-3), this appears to be independent of the increase or decrease in insulin sensitivity. However as pregnancy advances in the second and third trimesters, there is a compensatory increase in insulin secretion with an increasing glucose load. Further variations in the maternal insulin response are observed according to the degree of maternal obesity.[12] For women who are lean prior to pregnancy, the mean insulin concentration and overall insulin response are more pronounced compared to obese controls. Additionally, for obese subjects, there is an increase in insulin clearance later in pregnancy with an observed increase in endogenous basal glucose concentration.[13,14] The observation by Catalano et al. of an increase in fasting HGP in nondiabetic lean subjects, despite the anticipated increase in fasting insulin concentration, suggests that central hepatic insulin sensitivity is diminished as pregnancy advances. For obese subjects, hepatic insulin sensitivity was reduced further because of less suppression of HGP during insulin infusion.

Bergman postulated that in normal individuals, the sensitivity–secretion relationship could most efficiently be expressed as a rectangular hyperbola.[15] In such a hyperbolic representation,

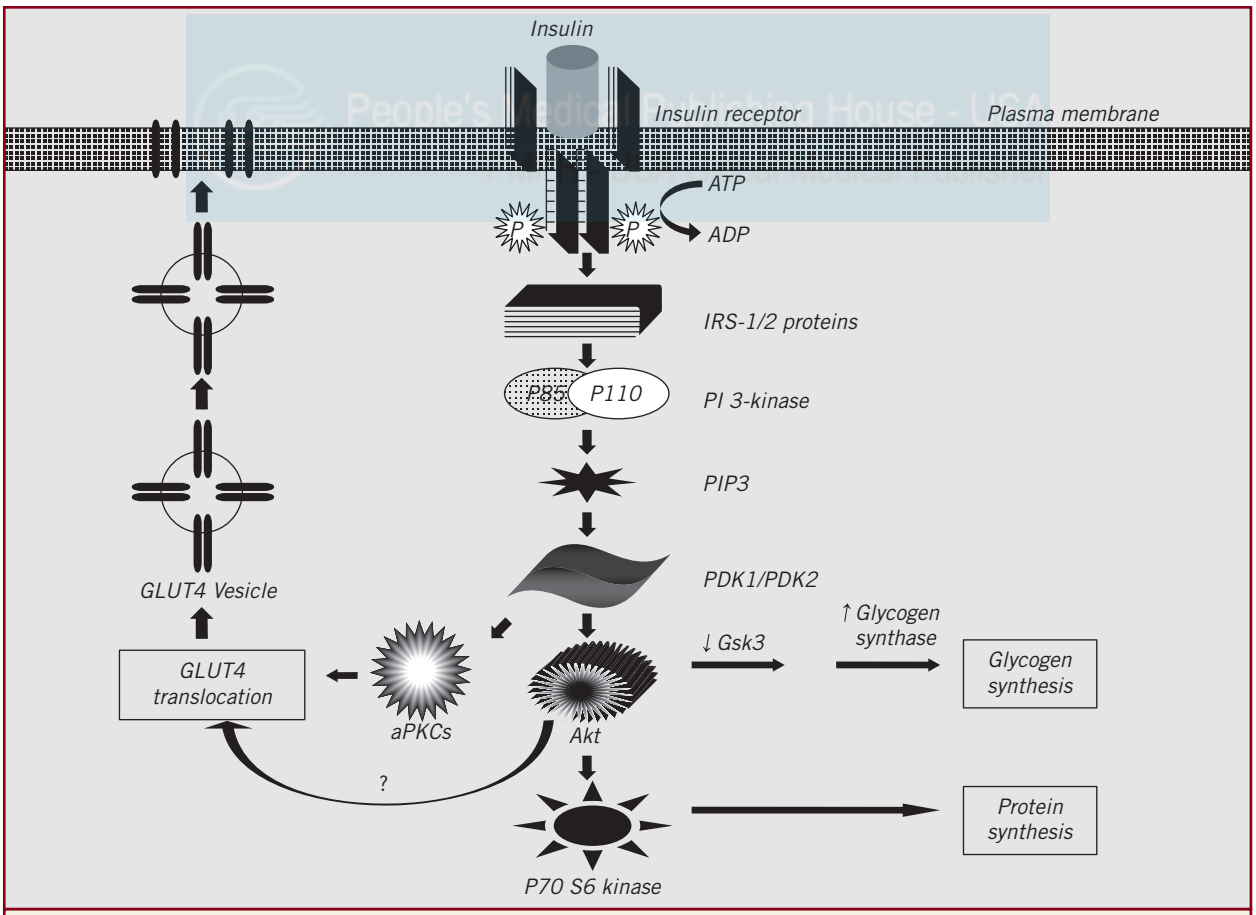

Figure 21-1 Insulin-signaling pathway.

the product of insulin sensitivity and insulin secretory response (ISR) would equal a constant, the disposition index (DI). Simply stated, the DI is a measure of the ability of the β-cells to compensate for insulin resistance. Others have confirmed this hyperbolic relationship.[4,16] The DI then provides a quantitative and convenient approach to studying insulin dynamics. This fixed relationship between insulin response and insulin resistance by Bergman has also been observed in pregnancy.[17] The Bergman minimal model employs mathematical modeling to derive an estimate of insulin-mediated glucose disposal from a frequently sampled intravenous glucose tolerance test (FSIGT). The time course of plasma glucose is fitted using nonlinear least-squares methods with plasma insulin values as a known input to the system.[18] Similarly, the euglycemic-hyperinsulinemic clamp uses the glucose infusion rate required to maintain euglycemia during a constant insulin infusion to estimate insulin resistance.[19] The modified FSIGT has been shown to have a strong positive correlation ($r = 0.89$) with the clamp method.[20] Others have shown insulin sensitivity values, calculated from the reduced sampling insulin-modified protocol, to correlate significantly with those obtained with the "clamp" across the spectrum of glucose tolerance.[21] Compared to the clamp technique, other methods estimating insulin sensitivity have been described including the IS_{OGTT}, IS_{QUICK}, and IS_{HOMA}. Kirwan et al. validated these indices in pregnant women with normal glucose tolerance and found significant correlations between IS_{CLAMP} and IS_{OGTT} ($r^2 = 0.74$), which was noted to be superior to the IS_{QUICK} and $IS_{HOMA.}$ They further evaluated IS_{CLAMP} and IS_{OGTT} throughout pregnancy. The prepregnancy period revealed a correlation of $r^2 = 0.63$; early pregnancy $r^2 = 0.80$; late pregnancy $r^2 = 0.64$. The data suggest that estimates of insulin sensitivity from the IS_{OGTT} during pregnancy are significantly more accurate than those obtained from fasting glucose and insulin values.[22]

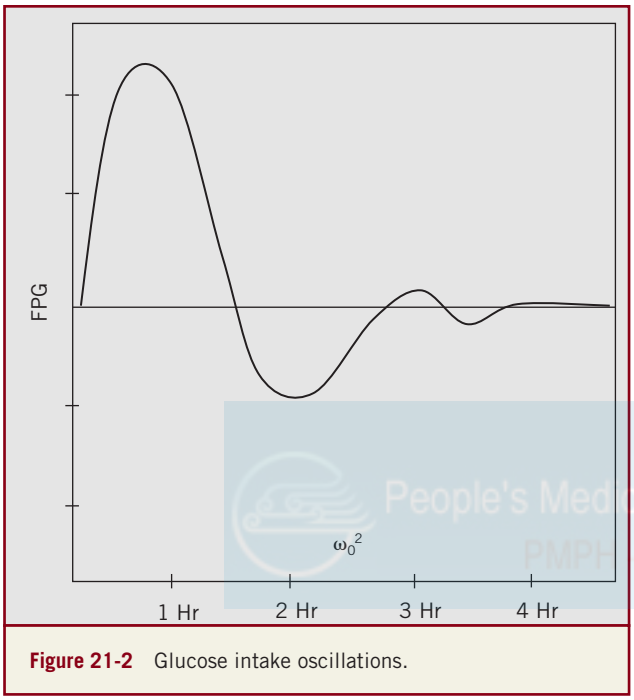

Figure 21-2 Glucose intake oscillations.

First reported by Spellacy and Goetz, there is a normal increase of insulin resistance near mid pregnancy, which continues through the third trimester. Compared to the prepregnancy state (Figure 21-4), there is a paradoxical initial improvement in insulin sensitivity early in pregnancy with a significant reduction in later pregnancy.[23,24] There is also an observed difference in the DI in early pregnancy as compared with either pregravid or late gestation (Figure 21-5). Hence, the increase in insulin sensitivity coupled with an increase in insulin response in early gestation suggests an independent metabolic adaptation of both β-cell function and peripheral insulin resistance in early gestation.

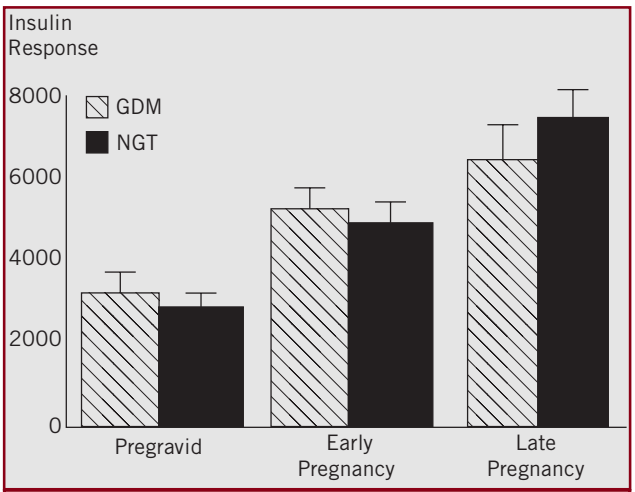

Figure 21-3 There is a significant increase in insulin response in early pregnancy, both in women with normal glucose tolerance (NGT) and in women who will develop gestational diabetes mellitus (GDM).

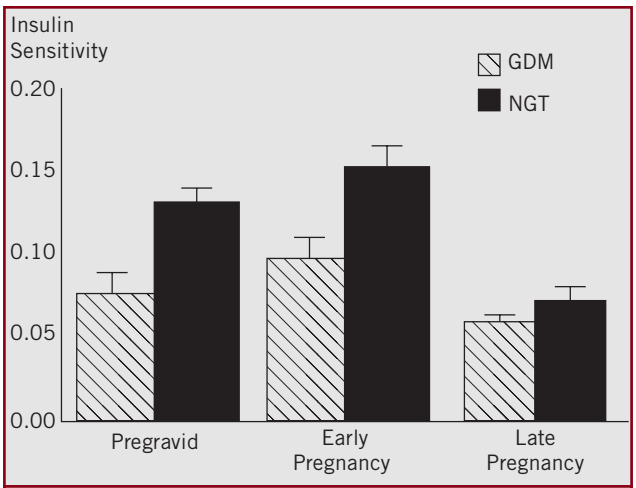

Figure 21-4 There is an increase in insulin sensitivity from pregravid through early gestation in both women with normal glucose (NGT) and women who will develop gestational diabetes (GDM).

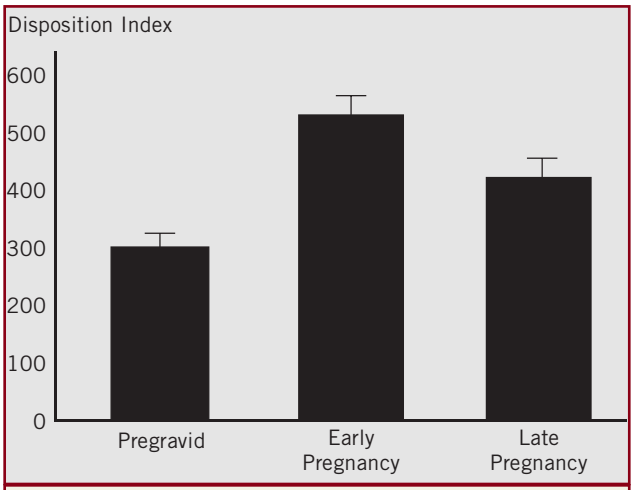

Figure 21-5 There is a significant increase in the disposition index in early gestation compared with pregravid and late pregnancy measures. These data are based on data from Figures 21-3 and 21-4.

The initial improvement in insulin sensitivity early in pregnancy with a marked reduction later in gestation is true for women with and without GDM. When evaluating lean and obsess women, Catalano et al. noted a 56% increase of insulin resistance in lean women and a 47% increase in obese gravidas using the euglycemic-hyperinsulemic clamp method.[12,25] Several etiologies of the progressive insulin resistance of pregnancy have been described. Both increasing maternal adiposity and the insulin-desensitizing effects of the hormonal products of the placenta have historically been linked to the diminished insulin sensitivity of pregnancy (such as human placental lactogen, progesterone, and estrogen). This is supported by the observation that insulin sensitivity rapidly improves after delivery. More recent evidence supports other mediators of insulin resistance, such as leptin, tumor necrosis factor-α (TNF-α), and resistin.[26] Catalano et al.[27] demonstrated increases in insulin resistance that correlated with TNF-α. TNF-α has also been shown to have a positive correlation with both body mass index (BMI) and hyperinsulinemia,[28] whereas infusion of TNF-α decreases insulin sensitivity in skeletal muscle cells. In a regression analysis including leptin, HPL, cortisol, human chorionic gonadotropin, estradiol, progesterone, and prolactin, TNF-α was the strongest predictor of insulin sensitivity.[29] In addition to other cytokines, the placenta produces TNF-α, with the majority transported into the maternal circulations. Other factors, such as circulating free fatty acids and other inflammatory mediators (such as C-reactive protein [CRP] and interlukin-6) may also contribute to the insulin resistance of pregnancy, particularly for obese women.[30] More recently, using samples selected from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) trial, Lowe et al. observed that levels of inflammatory mediators, such as adeponectin, plasminogen activator inhibitor type 1 (PAI-1) and CRP varied in a constant manor across the spectrum of increasing levels of maternal glucose.[31]

GDM

Simply stated, GDM is a form of hyperglycemia that results from an insulin supply that is inadequate to maintain glucose homeostasis. The majority of women with GDM appear to have β-cell dysfunction. However, the etiology of inadequate β-cell responses diverse and includes autoimmune related destruction, monogenic causes, and in the setting of diminished insulin sensitivity.

Outside of pregnancy, the two major classifications of diabetes are type 1 and type 2. Type 1 DM results from autoimmune destruction of pancreatic β-cell, and accounts for 5%–10% of diabetes in the general population.[32] Initial investigations reported 10%–35% of GDM patients to have circulating antibodies against pancreatic islet cells.[30,33–36] This led to the opinion that GDM may be within the spectrum of type 1 DM. However, subsequent investigations using specific monoclonal antibodies noted only 1%–2% of GDM women to have circulating antibodies.[36] For this small subset of patients, the abnormal glucose homeostasis observed in pregnancy results from inadequate insulin secretion from autoimmune damage of β-cells and likely represents previously undiagnosed or evolving type 1 DM.

Monogenic diabetes refers to the genetic causes of diabetes and includes two forms. The most common is maturity-onset diabetes of youth (MODY), an autosomal dominant disease with associated mutations in the glucokinase gene. Other less common genetic mutations are noted in mitochondrial DNA, often observed with other clinical syndromes. MODY is characterized by abnormalities of β-cells mass or function with two discrete subtypes: MODY1 and MODY2.[37] For both subtypes, onset occurs in young adulthood and patients tend not to be obese or insulin resistant. Mutations that are associated with MODY subtypes have been reported in women with GDM including mutations in genes coding for glucokinase (MODY2), hepatocyte nuclear factor 1-α (MODY3), and insulin promotor factor 1 (MODY4).[38–42] In general, MODY mutations account for less than 10% of GDM subjects, and likely represent a subset of those women with undiagnosed pre-GDM.

For the vast majority of patient diagnosed with GDM, the pathophysiology is far more similar to type 2 DM with diminished skeletal muscle and hepatic sensitivity to insulin, and inadequate β-cells response to an increasing glucose load. Similar to women without GDM, there is a natural decrease in insulin sensitivity observed for GDM subjects over pregnancy. For women with GDM, the observed increase in insulin resistance is greater when compared to women with normal glucose testing and there is a diminished response to insulin for peripheral glucose uptake and suppression of HGP.[12,30] Additionally, the observed insulin response to a given glucose load is muted for GDM patients, particularly in later pregnancy. Postpartum, women with GDM have a persistent insulin resistance and diminished insulin response, providing further support that these subjects are within the spectrum of type 2 DM.

Several authors have used the Bergman minimal model to determine variations in the DI and insulin sensitivity for subjects with and without GDM in both early and late pregnancy. In this model,[20] for nonpregnant glucose-tolerant women, a hyperbolic relationship between insulin sensitivity (S_I) and insulin secretion, for both first (Φ_1) and second phase (Φ_2) insulin response is observed. When comparing pregnant (late gestation) and nonpregnant women with normal glucose tolerance testing, Φ_1 was not related to S_I (Figure 21-6) whereas Φ_2 was (Figure 21-7), however

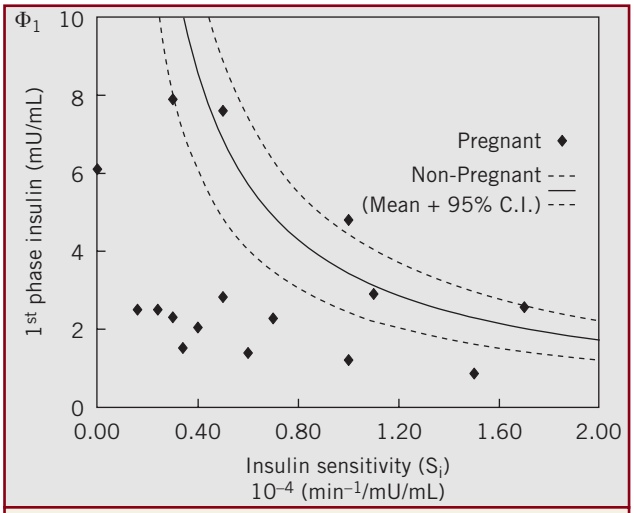

Figure 21-6 Glucose tolerant women Φ_1.

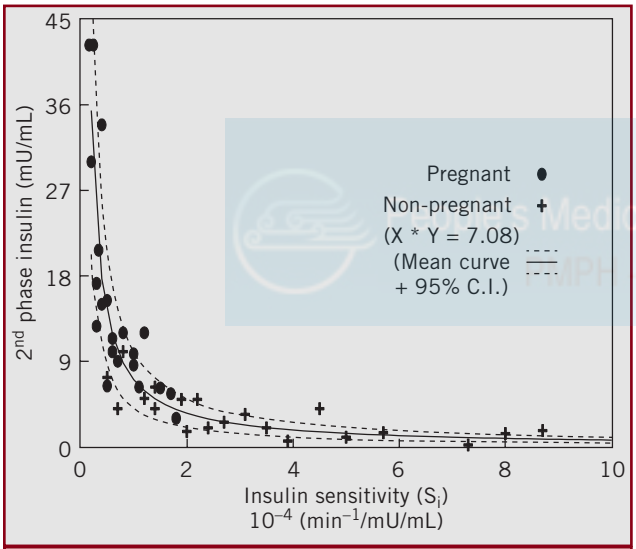

Figure 21-7 Normal glucose tolerance Φ_2.

the calculated DI was constant for these women (DI = 7.08), with a shift toward a decreased S_I during pregnancy. The loss of the hyperbolic relationship between S_I and Φ_1 for 75% of gravidas was felt to be due, at least in part, to the effect of the fetal compartment on lowering fasting glucose in pregnancy, suppressing insulin storage and initial release. When comparing women with and without GDM, further alterations in glucose metabolism can be found.[43] SI is significantly decreased in obese GDM gravidas compared to those with normal glucose tolerance (NGT), whereas lean GDM subjects have a lower Φ_1.[12,23,25,44] In studies that used a modified FSIGT over the late second and early third trimesters prior to treatment, both lean and obese gravidas showed a decreased capacity to secrete insulin even when adjusted for the level of glycemia. Using a graphic representation to express the DI (Figure 21-8), both groups demonstrated a decrease in Φ_1, well below the 95% CI for normal pregnancy. However, 44% of

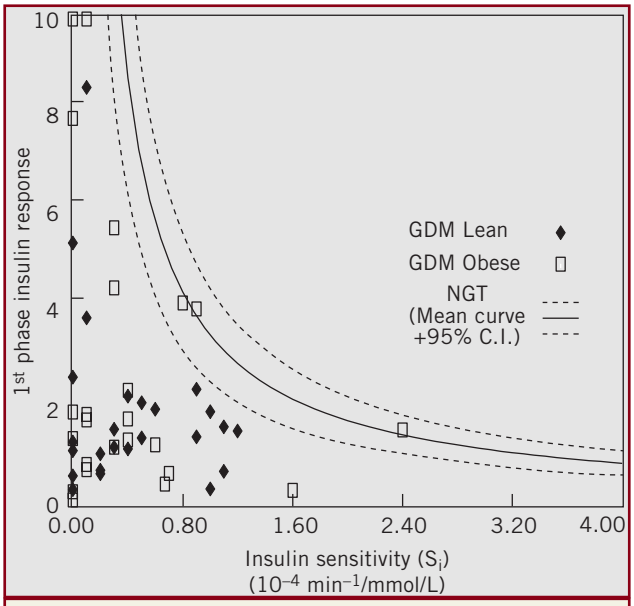

Figure 21-8 GDM studies Φ_1.

lean and 22% of obese gravidas measured at or above the normal curve, consistent with the incidence of metabolic abnormalities found postpartum[45–48] and the incidence of type 2 DM in former lean and obese GDM subjects.[49]

Ryan et al.[23] studied normal pregnant women at 28 weeks gestation (n = 5) and GDM at 36 weeks (n = 5), all with the euglycemic clamp technique. They found that S_I was lower in three of the five GDM women. Their patients were obese and had elevated fasting levels (>130 mg/dL) that may have indicated overt diabetes. They did find that insulin infusion approached normal levels when good glycemic control was obtained in two subjects. Catalano et al.[25] studied nonobese GDM (n = 8) prior to pregnancy, at 12–14 weeks, and 34–36 weeks gestation using the euglycemic clamp. They found mildly increased sensitivity early in pregnancy with a large fall by late gestation. GDM gravidas increased Φ_1 as did NGT, but not in proportion to the decrease in S_I; there was no difference from normal levels of Φ_2. Kautzky-Willer et al.[45] studied normal lean pregnant women (n = 9) and lean GDM (n = 10) using an unmodified FSIGT. They studied patients between 26 and 31 weeks gestation, prior to institution of therapy. They found S_I 50% lower in GDM. Both Φ_1 and Φ_2 were reduced compared to NGT in the study. Berkus et al.[43] studied a larger group of GDM subjects, matched for BMI and gestational age (26–32 weeks), and prior to any therapy. An insulin-modified FSIGT was used because of the blunted insulin release in pregnancy to assure adequate insulin for the calculation of resistance. They were able to demonstrate a combined defect in insulin release and sensitivity that characterizes both lean and obese GDM women (Figure 21-8). Φ_2 was similar to NGT except in subjects likely to have overt diabetes (Figure 21-9).

As pregnancy advances, there is a decrease in the observed fasting glucose concentration for women with GDM. This is likely due to the increase in fasting insulin production observed for lean and obese gravidas with GDM. Paradoxically in late pregnancy, glucose production (particularly HGP) increases in

women with GDM.[12,14] This suggests an impaired hepatic sensitivity to progressively increasing insulin levels. Studies of human skeletal muscle and adipose tissues have observed signaling defects of insulin-sensitive receptors, including GLUT4 transporter that support an impaired tissue response to increasing insulin concentrations. For any pregnant women, there are observed changes within the insulin-signaling cascade for GLUT4, with additional abnormalities noted for women with GDM. As noted earlier, all pregnant women have a decreased expression of IRS-1 within the GLUT transporter system. The decreased expression of IRS-1 is matched by the observed progressive decreased ability of insulin to stimulate the normal signaling of GLUT4 to approach the cellular membrane and initiate glucose uptake. For women with GDM, there is a marked decrease of insulin-stimulated phosphorylation of the receptor, which results in an observed 25% reduction in glucose transport activity. Therefore, GDM does not appear to result from an abnormality of the insulin receptor (GLUT4) within skeletal muscles.[50] Rather women with GDM have alterations of the insulin-signaling pathway,[51–54] subsequent abnormal location of the GLUT4 transporter,[55] reduced expression of PPARγ,[51] increased expression of the membrane glycoprotein PC-1,[53] and reduced insulin-mediated glucose transport,[54,55] all which may contribute to abnormal glucose control.

Little data is known about the genetics of GDM. For women with GDM, variants in allele frequency have been observed within genes coding for islet-specific promoter of glucokinase,[54] calpin-10,[56] the sulfonylurea receptor 1,[57] and the B3 adrenoreceptor. Radaelli et al. reported that women with GDM, compared to women with type 1 DM, had 49 alterations in gene expression at key steps of energy metabolism within the placenta. The majority of those alterations were observed in pathways related to lipid metabolism (67%) and glucose pathways (9%). On the basis of this data, the authors concluded that genes that code for feto-placental lipid metabolism are increased with GDM and may be essential in the development of observed clinical outcomes such as fetal macrosomia.[58]

POSTPARTUM

As noted earlier, GDM likely represents a continuum within the spectrum of disease that ultimately manifests as type 2 DM. After delivery, when the placental mediators of insulin resistance subside, women who were diagnosed with GDM continue to have increased insulin resistance compared to normal controls (Figure 21-4). This supports the hypothesis that women with GDM have a chronic component of insulin resistance.[45–48,50,59,60] Therefore, it is not surprising that long-term follow-up studies of women with GDM showed that the incidence of eventual overt diabetes was 47% in obese women and 26% in women of normal weight.[61] The likely contributors to this chronic insulin resistance include common risk factors for type 2 DM including obesity, weight gain, and age in addition to biochemical mediators such as leptin,[62] TNF-α,[63] and CRP.[64] Often, the observed hyperglycemia of pregnancy is limited at first to only pregnancy, with up to 90% women having normal glucose testing immediately postpartum.[65] However, over time, the majority of women (70%) diagnosed with GDM will have a positive test for overt diabetes.[66]

Homko et al.[59] found that women with GDM during late pregnancy had a large β-cell defect with their first phase insulin response decreased compared to controls. Following delivery, ISR was decreased 40% from levels during pregnancy and not significantly lower than controls. However, this degree of insulin response was not normal as women with previous GDM were more resistant than controls. Subsequent investigations of postpartum changes in insulin sensitivity for patients with GDM have been performed.[67] Berkus et al. reported on 32 previous GDM patients that underwent a repeat FSIGT three months postpartum, all of whom had a normal 75 g 2-hour oral glucose tolerance test (OGTT) by WHO criteria. Glucose values were greater for obese (BMI > 29) versus lean and the area under the curve (AUC) glucose was also greater for previous GDM versus NGT controls. Plotting out the DI for the postpartum group (Figure 21-10) demonstrated that 69% lean and 86% obese subjects had DI below the normal curve. Thus, they were unable to release the appropriate insulin for their degree of insulin sensitivity. However, 80% were able to

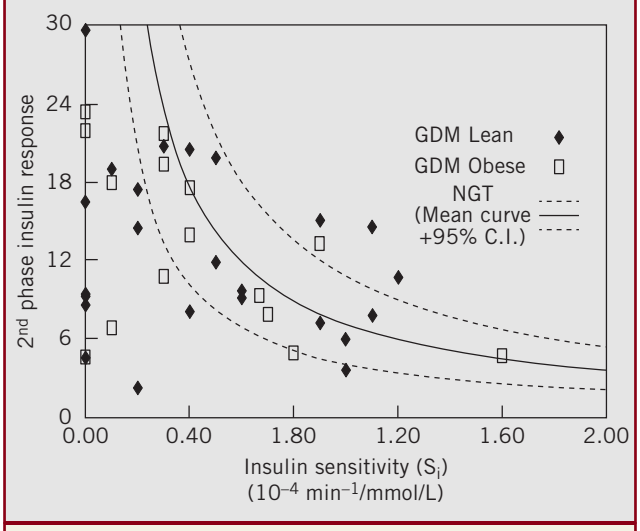

Figure 21-9 GDM studies Φ_2.

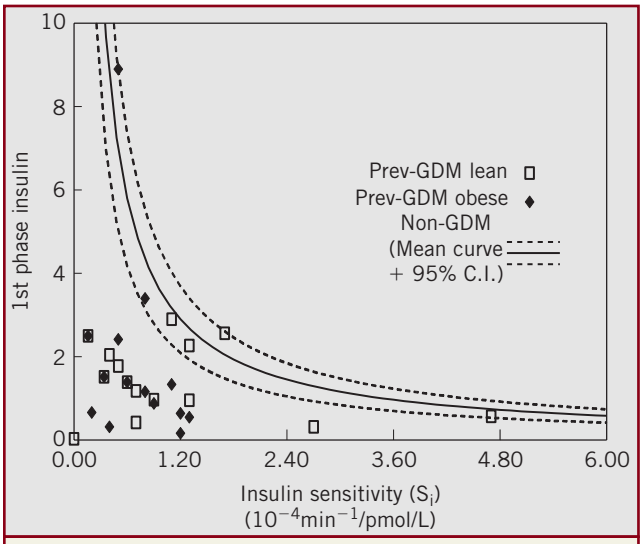

Figure 21-10 Postpartum studies Φ_1.

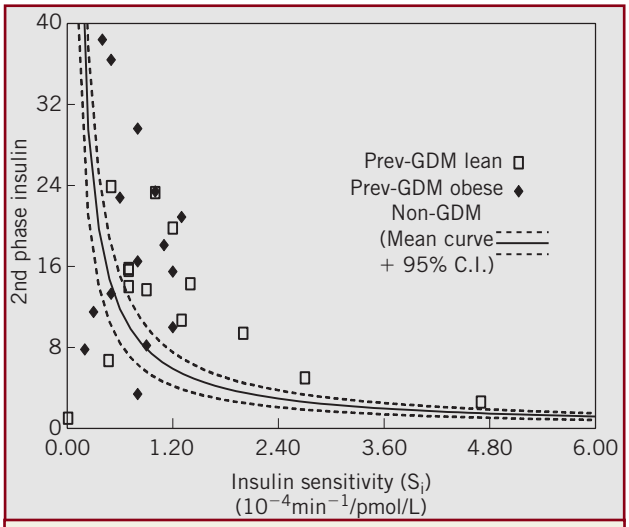

Figure 21-11 Postpartum studies Φ_2.

secrete adequate amounts of insulin in the second phase for the degree of insulin resistance as well as the increased glucose concentrations (Figure 21-11). This pattern is characteristic of type 2 DM and is consistent with the epidemiologic evidence of a high incidence of subsequent diabetes in former GDM women.

Longitudinal studies of the pathophysiology of overt diabetes that develops subsequent to GDM reveal some interesting data. Several factors have been observed to contribute to progressive β-cell underperformance including weight gain, progressive hyperglycemia, and additional pregnancies.[68,69] For most women, β-cell function can continue to preserve glucose homeostasis until the DI becomes significantly diminished (less than 15% of normal). After this threshold is breached, additional decreases in the DI manifest as progressively poor glucose control. Interestingly, treatment at this stage of disease with insulin therapy, prior to the development of true diabetes, results in both a downregulation of insulin secretion[70] and a preservation of β-cell function with a reported decrease in the risk of diabetes.[71]

SUMMARY

The alterations in maternal metabolism resulting in the development of GDM are but a perturbation of the normal metabolic physiologic changes during pregnancy. The normal increases in insulin response in early pregnancy are necessary for the anabolic changes in early pregnancy, that is, adipose tissue accretion is necessary for the caloric demands of the third trimester and lactation. The increased insulin resistance observed in late gestation allows for nutrient transfer, not only glucose but lipids and amino acids as well, required for fetal growth and development. For the vast majority of GDM observed today, the increases in maternal obesity, malnutrition, and lack of physical activity result in a poor metabolic profile prior to conception. As the metabolic changes in pregnancy occur regardless of the maternal pregravid metabolic condition, it is not surprising that the number of women with GDM continues to increase, regardless of the criteria used in the diagnosis. If there is a silver lining in this metabolic cloud, it is that the diagnosis of GDM provides an opportunity to institute prevention early in the course of type 2 DM disease progression. Lifestyle intervention as reported in the Diabetes Prevention Programs[72] demonstrate that prevention or at least delay of type 2 DM is possible for this high-risk population.

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Gestational Diabetes

The Consequences of Not Treating

22

Oded Langer, MD, PhD

*To **LOOK** is one thing, to **SEE** what you are looking at is another, to **UNDERSTAND** what you see is a third, to **LEARN** from what you see is still something else, but, to **ACT** on what you learn is all that really matters*

—Anonymous

Key Points

- Gestational diabetes mellitus (GDM) in all severity levels (from one or more abnormal values) is associated with decreased insulin sensitivity and secretion
- The majority of GDM women are prone to develop type 2 diabetes later in life
- There is significantly higher adverse neonatal outcome as a sequelae of not treating GDM
- All GDM severity levels will result in adverse neonatal outcome
- Short-term neonatal complications include increased perinatal mortality; metabolic, respiratory, and hematological complications; and neonatal trauma
- Long-term neonatal implications include metabolic syndrome, obesity, future diabetes, and intellectual impairment
- The treatment of women with GDM and achievement of targeted levels of glycemic control will enhance pregnancy outcome

THE GDM CONTROVERSY

It is axiomatic that type 1 and type 2 poorly controlled diabetic women have a significant increase in adverse perinatal outcome in comparison to nondiabetic patients. Therefore, it is reasonable to assume that similar adverse outcomes will result in gestational diabetes (GDM) as it is almost a mirror image of type 2 diabetes. Since the late 1960s, when O'Sullivan first suggested the term "gestational diabetes," controversy continually surrounded this clinical entity even though GDM is associated with adverse pregnancy outcome, that is, macrosomia, birth trauma, and neonatal hypoglycemia. Opinions and anecdotes have been more prolific than research generated data on this issue. There was no consensus regarding diagnostic criteria, the utility of universal screening or the association of GDM with perinatal morbidity and mortality. For example, Jarrett concluded that GDM is "a non-entity" whose only clinical association is with an increased maternal risk of subsequent diabetes.[1] The Scottish Intercollegiate Guidelines Network (SIGN) published a document regarding the management of diabetes in pregnancy in 2001. They reiterated that there was no consensus on the definition, management, or treatment of GDM and that the most appropriate strategies for screening, diagnosis, and management of asymptomatic GDM had remained controversial. A document published in the United Kingdom in October 2003 from the National Institute for Clinical Excellence suggested that available evidence did not support routine screening for GDM. The Society of Obstetricians and Gynecologists of Canada suggested in their guidelines to target screening for GDM to high-risk women. They included obesity among the risk factors, using a cutoff body mass index (BMI) of 27 kg/m^2. In a letter to the editor, Hunter and Milner stated that "gestational diabetes is a diagnosis still looking for a disease." According to these physicians, GDM was not convincingly associated with increased perinatal mortality or morbidity, and macrosomia per se, regardless of definition, is not a morbid condition.[3] Greene in an editorial in the *New England Journal of Medicine* (2001) questioned if GDM is a disease.[4] In contrast, Beard and Hoet[5] in a review article concluded that GDM is a clinical entity associated with a significant incidence in diabetes in the later life of the mother and an increase in fetal and neonatal morbidity.

Lack of agreement on universal screening, diagnostic criteria, and the methodology for glucose tolerance testing led to inconsistency in the results of published studies. Opposing positions were not the result of authors' evidence-based data (randomized controlled trials [RCTs]) that could have provided the ultimate answer, but were instead based on opinions lacking evidence. However, randomized controlled studies may have been deemed unethical.[6] Faced with an ethical dilemma over the use of a randomized design, a well-designed cohort and case-controlled study is an ethical and research appropriate alternative to an RCT.

GDM is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. The definition applies regardless of treatment modality and/or the persistence of the condition after pregnancy when it will be termed type 2 diabetes when indicated. Empirical attempts were made[7–9] to address the controversy surrounding this entity. If GDM was *not a disease*, then we liberated thousands of women from unnecessary treatment; if GDM was found to be *a disease*, practitioners could then provide interventions that would positively impact perinatal outcome. Both assumptions had the potential to either decrease cost of care when treatment is not warranted or enhance quality of care by decreasing morbidity.

In approaching the debate if GDM was a clinical entity, three conditions needed to be demonstrated:

1. Presence of pathophysiology
2. Significant adverse outcome, that is, maternal and/or fetal
3. Treatment that improved adverse outcome

CHANGE FROM PHYSIOLOGY TO PATHOPHYSIOLOGY

Identification of the primary metabolic disturbance in GDM would facilitate the development of interventions aimed at prevention as well as treatment. GDM may provide the ideal model for investigating the primary defect, which leads to the development of type 2 diabetes. Human pregnancy is an insulin-resistant condition. Although there is a four- to fivefold range of insulin resistance in the general population, there is a relatively uniform 40%– 50% increase (from the pregravid condition) in insulin resistance and increase in insulin secretion in obese patients of 60% in the first phase of secretion and 130% in the second phase; for lean individuals, a similar increase of 200%–250% in both phases of insulin secretion occur during pregnancy. These alterations in insulin have been previously ascribed to a variety of reproductive hormones such as human placental lactogen, cortisol, progesterone, and estrogen. More recent data have implicated adypocyte/placental secreted factors such as cytokines, in particular tumor necrosis factor-α (TNF-α) and leptin, as active candidates in the alteration of insulin sensitivity in pregnancy. Adiponectin belongs to the family of adipocytokines, which also includes leptin, TNF-α, resistin, interleukin-6 (IL-6), and others.[10] Adiponectin is associated with obesity, diabetes, cardiovascular disease, and dyslipidemia.[11–13] From a metabolic standpoint, adiponectin produces an insulin-sensitizing effect on skeletal muscle, adipose tissue, and liver.[14] It has been demonstrated that the level of adiponectins in class A2 and B GDM are associated with suppressed levels of adiponectins, similar to that found in other insulin-resistant states (type 2 diabetes and obesity).

Retnakaran et al.[15] reported that C-reactive protein (CRP) levels in late pregnancy relate to pregravid BMI and not to GDM per se. Assuming that the CRP concentrations in late gestation are a marker of insulin resistance, then a woman's pregravid BMI may be the strongest clinical indicator of the degree of her insulin resistance, even in late gestation. The lack of relationship of CRP to GDM may reflect the wide variation of pregravid BMI to inflammation/insulin resistance rather than the relative uniform decreases observed during pregnancy.[16]

Another factor that may contribute to increased insulin resistance during pregnancy is the increase in body fat or change in body fat distribution that begins in early gestation. It is well-established that obesity per se causes insulin resistance.[17] It has been shown that total oxidative and nonoxidative glucose metabolism is inversely related to increased visceral-to-subcutaneous fat ratio in obese women and to total fat content in lean women.[18] Others have demonstrated decreased insulin sensitivity in subjects with a central pattern of fat distribution. Whatever the cause for increased insulin resistance during pregnancy, in women who maintain normal glucose tolerance, it is offset by a 3- to 3.5-fold increase in insulin secretion.[19] Therefore, the degree of insulin resistance during late gestation appears to be dependent primarily on pregravid maternal insulin resistance, which is quite variable, and secondarily on the 40%–50% increases mediated through placental factors.

In 1981, Bergman et al.[20] proposed that there is a predictable relationship in the shape of a rectangular hyperbola between the quantity of insulin produced by β-cells and the sensitivity of tissues to the glucose-lowering effects of that insulin. Kahn et al.[21] demonstrated that such a relationship is present across a wide range of insulin sensitivity in people with normal glucose tolerance. A hyperbolic relationship exists between insulin sensitivity and several measures of β-cell insulin release in women with impaired glucose tolerance (IGT).[22] The amount of insulin released at a given level of insulin resistance is lower in people with abnormal compared with normal glucose tolerance.[23,24] Although GDM is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy,[25] the definition applies whether the condition persists after pregnancy, but does not preclude the possibility that the glucose intolerance may have predated the pregnancy. Women who develop GDM are, in fact, genetically predisposed to develop type 2 diabetes, as they tend to have a strong family history of the disease. Some stressors associated with pregnancy probably trigger them to develop overt disease sooner than if they had not become pregnant.

GDM is generally diagnosed at 24–28 weeks gestation and subsides to a subclinical state after delivery. It generally recurs with subsequent pregnancies and is clearly the harbinger of abnormal glucose metabolism in later life.[19,26–28] O'Sullivan's 15-year follow-up study of women with previous GDM showed that the incidence of type 2 diabetes was 26%–47%.[27] The incidence of type 2 diabetes in a control population with normal glucose tolerance test results during pregnancy was only 2%–4%. Others have found approximately 20% of patients with GDM who have IGT at six weeks postpartum.[19,28–31]

Similar to other groups genetically susceptible to type 2 diabetes, women with previous GDM and normal glucose tolerance have been shown to have defects in glucose metabolism. Using the hyperinsulinemic-euglycemic clamp technique, Catalano et al.[28] demonstrated insulin resistance in 50% of subjects with normal glucose tolerance and previous GDM. This was primarily due to decreased nonoxidative glucose disposal. Ward et al.,[32] using the Bergman intravenous glucose minimal model technique also found evidence of increased insulin resistance in women with previous GDM. Unfortunately, neither Catalano nor Ward controlled for family history, so it is unclear whether family history

or previous GDM was the marker for these early abnormalities in glucose metabolism.

It is not too surprising that GDM develops in genetically susceptible women when they become pregnant. They probably have some degree of insulin resistance prior to pregnancy and normal pregnancy is associated with severe insulin resistance. Catalano et al.[19]found an approximately 21% decrease in insulin sensitivity occurring by 12–14 weeks gestation and a 56% decrease in insulin sensitivity occurring by 34–36 weeks. Others[18] have found similar results.

In summary, GDM is characterized by pathogenesis deviating from the normal physiology of pregnancy, which involves insulin resistance and decreased insulin secretion. Furthermore, similarity exists between the pathogenesis of GDM, IGT, and type 2 diabetes, which are probably one disease at different stages on the spectrum of glucose intolerance.

MATERNAL AND FETAL OUTCOME MEASURES

Each outcome variable needs to be weighed in terms of its potential for modification to enhance pregnancy outcome. For instance, targeting the desired level of glycemia with the appropriate treatment modality and control of weight gain may positively affect the rate of macrosomia, metabolic and respiratory complications, and so on. The unmodifiable variables will include maternal age, ethnicity, obesity, and genetic factors. Furthermore, certain outcome variables will be influenced by physician behavior based on legal and social pressures. These include cesarean section and neonatal intensive care unit (NICU) admissions , which will also be affected by the definition used for the given abnormality (i.e., hypoglycemia). Research studies need to report outcome variables both as univariant data and as multivariant analysis to show the net effect of each variable; this process controls for confounding effects.

Composite outcomes that combine several specific outcomes are often used as primary outcomes in obstetric studies. They in effect produce a single outcome. It is advantageous to use composite outcomes as they make trial designs more efficient. The most frequently cited reason for using composite outcome is that of statistical efficiency. The disadvantage is that they may be difficult to use and interpret. Even though the whole is equal to the sum of its parts, not all the parts carry equal weight. Each component should be presented as a secondary outcome so that readers can make up their own minds about the relevance of each outcome in the overall rate. Therefore, the reported rate of a composite outcome is affected by the outcome variables that have been selected for inclusion. Thus, the use of a composite outcome does not always lead to an increase in the evidence supporting a benefit for an intervention. Until standardized methods are available, researchers who decide to use a composite outcome in a clinical trial should carefully consider the rationale for selecting each component outcome for short- and long-term consequences.

Short-Term Effects of GDM

The adverse outcomes most commonly associated with GDM include increased perinatal mortality, macrosomia, shoulder dystocia, birth trauma, preeclampsia, cesarean section, neonatal hypoglycemia, hypocalcemia, hyperbilirubinemia, and polycythemia.

Long-Term Effects of GDM

When addressing the issue of the long-term effects of GDM, one must differentiate between the long-term maternal effects and the prognosis for the offspring.

The Mother

The increased risk of developing diabetes later in life in women with GDM is well known with the magnitude of the risk ranging from 20% to 50%, being lower in Caucasians and higher in Hispanic women, and women of Mediterranean or East-Asian descent and the Canadian Aboriginal population.[33–35] There is no evidence that the treatment of GDM will reduce this risk although recent data[36–38] suggest that the rate of progression to type 2 diabetes can be modified by lifestyle changes, thus underscoring a possible benefit for increased surveillance of this high-risk population.

The Neonate

Since Barker's primary epidemiologic studies in 1989[39,40] showing an inverse relationship between birth weight and mortality due to adult ischemic heart disease, it has become increasingly clear over the past decades that many fetal stressors may lead to fetal programming and the alteration of the normal developmental gene expression pattern. Research indicates that the child of the diabetic mother remains at increased risk for a variety of developmental disturbances: obesity,[41–44] IGT or diabetes,[45] and diminished neurobehavioral capacities.[46–52] Therefore, it would be reasonable to speculate that the process whereby a stimulus or insult (glucose toxicity and other metabolic fuels) acting at a critical period of development in early and during intrauterine life alters gene expression patterns for life.

GDM AND ITS EFFECTS ON OFFSPRING'S FUTURE OBESITY

Silverman et al.[53] demonstrated that the growth of offspring of diabetic mothers is similar to nondiabetic populations after 12 months. However, after age 5, there is a rapid weight gain and by age 8, almost half of the offspring of diabetic mothers weigh at or above the 90 percentile. In addition, a slight upward trend in height was noted. Pettitt et al.[54] in the Pima Indian population demonstrated that by 5–9 years of age, both macrosomic and normal-birth-weight infants of GDM mothers are more obese than normal-birth-weight offspring of nondiabetic mothers. Adiposity in children is strongly correlated with childhood hypertension (both systolic and diastolic) and resembles the metabolic syndrome albeit in evidence at a younger age. Moreover, the presence of hypertension in large for gestational age (LGA) infants was suggested as a cause for this condition in children.[55] In another study, Vohr et al. reported that LGA infants of GDM mothers had higher BMI waist circumference and abdominal skinfolds at 1 year compared to infants of nondiabetic mothers. The mean postprandial glucose value for the second and third trimester correlated with waist circumference ($r = 0.28$, $P < .04$) and subscapular

skinfold ($r = 0.37$, $P < .007$). They concluded that macrosomic infants of GDM mothers have unique patterns of adiposity that are present at birth and persist at age 1.[56]

COGNITIVE DEVELOPMENT IN CHILDREN OF DIABETIC MOTHERS

Several studies evaluated the association between cognitive development and metabolic fuels in preexisting and GDM. The research group at Northwestern University, Chicago tested 73 preexisting and 112 GDM infants for the relationship between maternal fasting plasma glucose and hemoglobin A1C (HbA1C) during the second and third trimesters on neonatal performance on the Brazelton neonatal behavioral assessment scale. The Brazelton scale has gained wide acceptance as one of the premier instruments for integrative characterization of nervous system function in the newborn period.[46,47] They found a significant correlation between glycemic control in three out of the four newborn behavioral dimensions on the scale. In each case, poor glycemic control was followed by poorer Brazelton ratings of the neonate. The results were neither different when gestational diabetic and pregestational diabetics were analyzed separately nor could they attribute them to various prenatal events such as asphyxia, neonatal hypoglycemia, or differences in socioeconomic status or ethnicity. Although the authors reported that their patients were well controlled, this statement is questionable as there was an approximate 30% rate of macrosomia (>4000 g), hypoglycemia, and hyperbilirubinemia. On the other hand, this perinatal outcome demonstrated the long-term complications one can anticipate when the level of glycemia is uncontrolled. Another study sponsored by the same group[57] evaluated the offspring of 95 preexisting diabetic women and 101 GDM subjects. The children were assessed using the psychomotor development index of the Bayley Scales of Infant Development at 2 years of age and the Bruininks–Oseretsky Test of Motor Proficiency at ages 6, 8, and 9 years. They reported that the children's average scores on the Bruininks–Oseretsky test at ages 6–9 years correlated significantly with β-hydroxybutyrate in maternal second and third trimesters. There was also a borderline association between children's scores on the psychomotor development index at age 2 and β-hydroxybutyrate. Similar findings were reported in another study.[58] Rizzo et al.[47] correlated measures of maternal glucose and lipid metabolism (fasting plasma glucose levels, HbA1C levels, episodes of hypoglycemia, episodes of acetonuria, and plasma β-hydroxybutyrate and free fatty acid levels) with two measures of intellectual development in the offspring using the Bayley Scales of Infant Development for 2-year-olds and the Stanford–Binet Intelligence Scale for 3–5-year-olds expressed as an average of the three scores. The children's mental development index scores at age 2 correlated inversely with the mother's third-trimester plasma β-hydroxybutyrate levels; the average Stanford–Binet scores correlated inversely with third-trimester plasma β-hydroxybutyrate and free fatty acid levels. Maternal diabetes during pregnancy may affect behavioral and intellectual development in the offspring. The associations between gestational ketonemia in the mother and a lower IQ in the child warrant continued efforts to avoid ketoacidosis and accelerated starvation in all pregnant women. Similar information was reported by Petersen et al. who suggested that first trimester intrauterine growth delay is associated with psychomotor deficit in the offspring at age 4–5. Presumably, such delays are driven from mothers who were in poor glycemic control (elevated HbA1C).[48,59] Sells et al.[51] reported that late entry into treatment programs in pregnancy in preexisting diabetic women resulted in lower scores on language measures and intellectual development through age 2 in comparison to women who maintained good control during pregnancy. Finally, Stenninger et al. reported that children born to mothers with diabetes (probably GDM), who subsequently developed neonatal hypoglycemia experienced long-term neurological dysfunction. The offspring were evaluated at age 8 and had more difficulties in validated screening tests for minimal brain dysfunction, were hyperactive, impulsive, and easily distracted. On psychological assessment, they had a lower developmental score in comparison to the offspring of normoglycemic diabetic women and nondiabetic control patients.[60]

In summary, the existing evidence clearly suggests that there is adverse neurological and cognitive outcomes in addition to the possibility of early development of metabolic syndrome (hypertension, obesity, and diabetes) when GDM is not treated or poorly managed. Of note, the adverse neonatal outcome is reported to be similar regardless of the type of diabetes. Finally, the maternal long-term implications for the future development of type 2 diabetes should be included in the morbidity spectrum of this disease.

DIABETES BEGETS DIABETES

In populations with a very high overall prevalence of the disease, type 2 diabetes in children and adolescents is reaching epidemic proportions. A study of type 2 diabetes among Pima Indian children showed that the rate increased significantly between 1967 and 1996.[61] The authors attributed weight gain in children as well as an increased frequency of exposure to diabetes in utero as the contributing factors. The in utero exposure to diabetes precipitates a cycle that causes fetal hyperinsulinemia; these results in an increase in fetal fat cells that trigger obesity and insulin resistance in childhood. These symptoms may stimulate IGT and the resultant diabetes in adulthood and eventually in pregnancy. This sequence of evidence was recorded not only in Pima Indian children but also in a heterogeneous population in Chicago where children of mothers with diabetes were found to be more obese and have higher rates of IGT than children of nondiabetic mothers.[45]

Many academicians attribute the epidemic of diabetes in younger people to genetics, our current propensity to gorge ourselves on higher fat diets and, compounding this insult to our bodies, with failure to exercise regularly. Public education on eating healthful diets and exercising regularly will address the needs of some. However, studies are beginning to emerge that the in utero environment is the source of this universal peril.[62] Siblings born after the mother's diagnosis of diabetes had a higher risk of diabetes than those born before the diagnosis. These results contrasted with siblings born to fathers with diabetes, in whom there were no significant differences between the siblings.

IS THERE AN ASSOCIATED INCREASED ADVERSE OUTCOME IN GDM?

In the past, there was scant evidence in the literature regarding outcome of pregnancy in untreated GDM. Roberts et al.[63] evaluated outcomes of women with untreated IGT during pregnancy and discovered an increased incidence of cesarean section. However, there were no differences in neonatal outcome compared with women with normal oral glucose tolerance test (OGTT). Ostlund et al.[64] studied 213 women prospectively who were identified with IGT during pregnancy and were undiagnosed and untreated. IGT was defined as fasting blood glucose level (<6.7 mmol/L) 121 mg/dL and two-hour blood glucose level (>9 and <11 mmol/L) 162–198 mg/dL. They compared the untreated IGT to control and treated GDMs. The rate of macrosomia (>4000 g) was 33%, 16%, and 30%; LGA 25%, 4%, and 25%, respectively. This finding demonstrates significant morbidity in the GDM and untreated groups. It also questions the efficacy of diabetic patient treatment. Similar findings were found relevant to metabolic complications, Erb's palsy and NICU admission. In their study, the obstetrician was not informed of the deviation in the glucose tolerance. They concluded that there is an increased independent association between cesarean section rates, prematurity and LGA, and macrosomic infants born to mothers with untreated IGT. The main problem in the Ostlund study is that the authors used a nontraditional definition for GDM, which was a modification of the Lind definition.[65] It is neither used in North America nor in the majority of European centers who follow the consensus agreement reached at the Fourth International Workshop on Gestational Diabetes.

Adams et al.[66] identified 16 cases of clinically unrecognized GDM diagnosed using the National Diabetes Data Group (NDDG) criteria and compared them to 64 nondiabetic controls. A third group consisted of 373 unmatched cases of GDM. The unrecognized group had 44% macrosomia, 44% LGA, 19% shoulder dystocia, 25% birth trauma, and 13% metabolic or respiratory complications. The nondiabetic controls and the unmatched GDM group had rates of macrosomia 8 versus 18%; LGA 5 versus 13%; shoulder dystocia 3 versus 4%; birth trauma 0 versus 0.5%; metabolic/respiratory complications 0 versus 10%, respectively. The study suggests that unrecognized GDM increases risks for neonatal complications such as LGA, macrosomia, shoulder dystocia, and birth trauma independent of maternal obesity and other confounding variables. Clinical recognition and dietary control of GDM are associated with a reduction in these perinatal morbid conditions. The limitation of this study is the small sample size; the results could have been affected by both alpha and beta errors.

Another series of studies was performed by the Toronto Tri-Hospital Gestational Diabetes Project.[67] In their first work, the investigators explored the function of the screening test. The second work involved looking at pregnancy outcomes for 3637 subjects without a diagnosis of GDM whose caregivers were blinded to the OGTT results. There was a direct relationship between OGTT results and a number of adverse pregnancy outcomes including cesarean delivery, neonatal macrosomia, and preeclampsia. When multivariate analysis was used to correct for the relative contribution of various other potential risk factors, such as maternal obesity and age, the OGTT results continued to have a significant independent impact. For example, for every 1.0 mmol/L (18 mg/dL) increment in the three-hour OGTT value, the likelihood of cesarean delivery rose by 10% even though the caregivers did not know the OGTT results. Similarly, for each 1.0 mmol/L (18 mg/dL) increase in the fasting plasma glucose level, the likelihood of macrosomia (birth weight $\geq$ 4000 g) increased by 100% even though the OGTT results were all in the presumed normal range.[68,69]

In another study, the OGTT results did not reach the NDDG threshold for GDM but did meet a lower set of thresholds that had been previously associated with increased morbidity.[70] In the untreated GDM group, the macrosomia rate of 29% was more than double the rates in the control and GDM groups (14% and 10%, respectively), whereas the cesarean delivery rate was 30%, similar to the rate in the GDM subjects. In these untreated pregnancies, however, cesarean delivery was significantly more likely when fetal macrosomia was present. These data demonstrate that the GDM treatment was apparently effective in reducing the rate of macrosomia, as undiagnosed and untreated women with mildly abnormal glucose tolerance manifested significantly increased fetal macrosomia.

Li et al.[71] randomly assigned 209 women into 3 groups based on the OGTT results. The first group "mild GDM" ($n = 75$) based on NDDG criteria were untreated. The second group was GDM, diagnosed after a 75-g OGTT by WHO criteria and was treated. The third group was normal, nondiabetic controls. The results showed a significantly higher rate of LGA, 29% in the untreated group (NDDG criteria) when compared to the nondiabetic control women. There was no significant difference in the rate of LGA between the treated GDM (WHO criteria) and the untreated group. This study again raises the issue that untreated GDM is associated with increased morbidity and questions the efficacy of glycemic control and the intervention in the treatment group. The relevance of this study is limited by the fact that the study group did not fulfill the diagnostic criteria for GDM. Thus, it is difficult to apply the results to the GDM population. In addition, neither the women nor caregivers were blinded to the OGTT results thus allowing the women to initiate dietary and other lifestyle modifications that could potentially have affected glycemic control while leaving the caregivers exposed to a potential labeling bias.

In summary, the above-mentioned studies were retrospective, with small sample sizes and the rate of metabolic and respiratory complications, and NICU admissions were not reported. Moreover, the majority of the studies mentioned previously used cesarean section as one of their primary outcome measures. Cesarean section, although associated with maternal morbidity (e.g., infection, bleeding), is a physician-driven decision rather than a complication of the disease. Cesarean section rate has evolved as part of the criteria to evaluate disease in general and GDM in particular. Today, cesarean section rates are continually rising with more repeat cesarean sections,[72] cesarean section by demand and elective cesarean section for breech delivery. It will not be surprising if in the near future, the rate of cesarean sections begins to reach 40%–50% for all deliveries. Indeed, many centers have already outstripped these numbers for both diabetic and nondiabetic patients. Therefore, cesarean section rate should not be used as an end point in GDM because the procedure is not directly related to the morbidity of the disease. It is directly related to physician decision making and performance and as such has become a self-fulfilling prophecy in the treatment of GDM, that

is, knowing one has a GDM patient gives the physician license to opt for cesarean delivery. This has been demonstrated by Naylor et al. that the cesarean section rate is not related to the rate of large infants in GDM. One of the problems inherent in studying the natural history of a treatable entity is that knowledge of the diagnosis may change the clinician's behavior. In the Toronto study, the authors looked at the cesarean delivery rate. Approximately 34% of patients with diagnosed GDM delivered by cesarean section, compared with 20% of women with normal results on screening tests and OGTTs. However, this 70% increase in the cesarean delivery rate was not caused by macrosomia. In fact, the macrosomia rate among pregnancies with diagnosed GDM was about 10%, similar to that in the control group.[73]

On the other hand, physicians are not automatically influenced by the GDM diagnosis. They instead weigh the presenting conditions of the disease. In one of our own studies, evaluating the intensified approach to the management of GDM, involving 1145 intensified treated GDM and 1316 conventional treated GDMs compared to 4922 nondiabetic controls, the cesarean section rate in the intensified treated patients was similar to the rate of the general population. In another study, we prospectively performed elective cesarean section for fetal weight >4250 g as a prophylactic measure to decrease the rate of shoulder dystocia. The study revealed that the cesarean section rate in the GDM population increased from 21% to 25% but the shoulder dystocia decreased from 2.6% to 1.1% (a decrease of 70%).[74,75]

Three recent studies[7–9] brought to a successful conclusion the controversy if GDM is a clinical entity. The authors,[7] in a case-controlled study, described pregnancy outcomes in a largely Hispanic population with three groups of patients: 555 women with untreated GDM matched with 1110 women treated for GDM as well as 1110 normal subjects. The untreated group was recruited after 37 weeks gestation, which in and of itself controls for lifestyle modifications such as diet that may influence pregnancy outcome. Patients and care providers were unaware of the GDM as the disease was diagnosed after 37 weeks gestation and included women with the entire spectrum of glucose abnormalities meeting the criteria for diagnosis. Thus, the fetus had been exposed to the glucose toxicity throughout pregnancy. The diagnostic criteria used in the study are one of two accepted criteria recommended in the last decade since its support by two international workshops on GDM.[76,77]

The power of the study[7] was sufficient to evaluate macrosomia, LGA, metabolic and respiratory complications, and NICU admissions. Furthermore, by developing a composite outcome, we were able to evaluate the overall neonatal disease (morbidity) in addition to specific morbidity components. The composite outcome included LGA, neonatal respiratory, hypoglycemia, hyperbilirubinia complications, shoulder dystocia, and stillbirth. Finally, selection into the nondiabetic comparison group was designed to control for potential confounding variables. Two nondiabetic control patients were matched to each untreated GDM on the basis of the following characteristics: ethnicity, parity, gestational age at delivery (within one week), obesity, severity of GDM, and number of prenatal visits. All the patients in the treated GDM group (n = 1110) were treated by the same care provider using the same management protocol. In addition, in the treated group, subjects used self-monitoring blood glucose with memory reflectance meters seven times daily to control for inaccurate reporting of their glycemic profile. We found that the perinatal outcome in the treated GDM group was comparable to the nondiabetic control group (n = 1110) in neonatal size, metabolic, respiratory, and labor complications. Although the cesarean section rate was significantly higher in the treated group, this in part may be attributable to the delivery protocol for diabetic patients when a weight estimation by ultrasound exams of 4250 g mandates elective cesarean delivery.[75] In the untreated group, we reported a 2- to 10-fold higher rate of adverse pregnancy outcome in comparison to nondiabetic subjects (Table 22-1).

The ACHOIS[9] was a multicentric 10-year randomized treatment trial of 110 women conducted at 14 centers in Australia. The enrollment was accomplished between 24 and 34 weeks gestation using a 75-g OGTT result of a two-hour glucose level between 7.8 and 11.0 mmol/L (140–198 mg/dL) and a fasting plasma glucose

TABLE 22-1 Selective Neonatal Outcomes Between Untreated and Nondiabetic Subjects

	Odds Ratio	95% CI
LGA	3.28	2.53–4.60
Macrosomia	2.66	1.93–3.67
Ponderal index	1.91	1.46–2.50
Shoulder dystocia	4.07	1.63–10.16
Hypoglycemia	10.38	6.15–16.56
Polycythemia	10.88	6.16–19.18
Hyperbilirubinemia	3.87	2.64–5.67
Pulmonary complications	3.43	1.87–6.27
Cesarean section	1.88	1.45–2.43
NICU < 24 h	3.99	2.47–6.43
NICU >24 h	4.11	2.37–7.10
Respiratory support	4.40	2.86–6.78

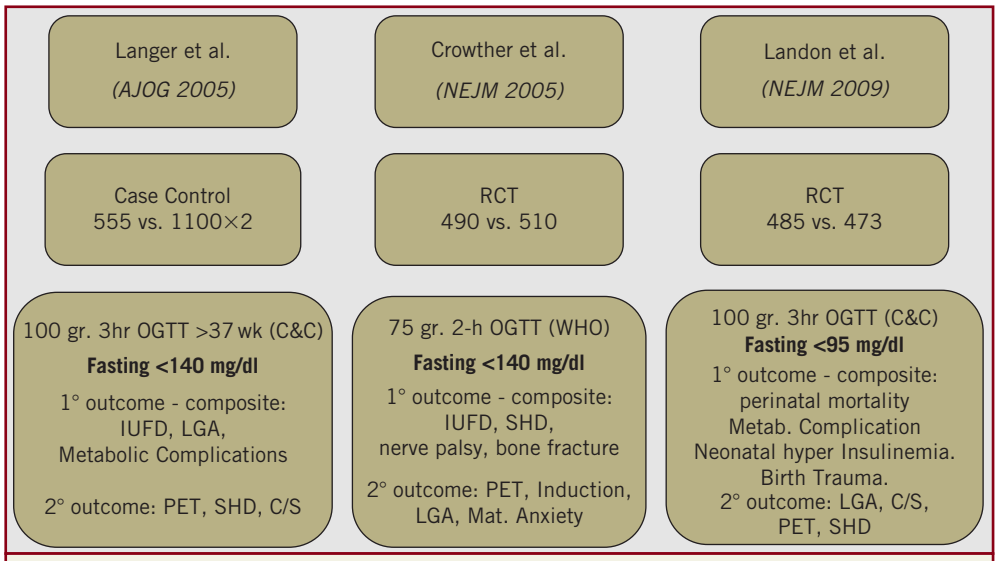

Figure 22.1 Study design.

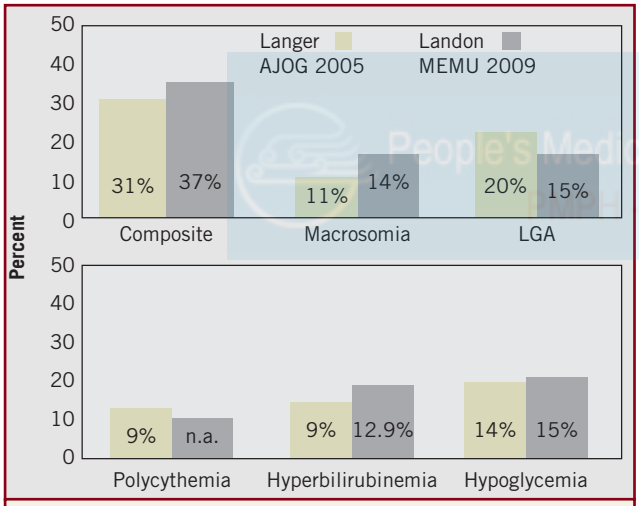

Figure 22-2 Untreated GDM's outcome with FPG < 95 mg/dL.

level less than 7.8 mmol/L (<140 mg/dL). The treatment group received dietary counseling and instruction in self-monitoring blood glucose testing four times daily (Figures 22-1 and 22-2). The targeted fasting value was 3.5–5.3 mmol/L (63–99 mg/dL). No glycemic data were reported. Insulin facilitated glycemic control in 20% of participants.

The third study was the NICHD MFMU Network[8] randomized control trial. Women, over a six-year period, were recruited between 24 and 31 weeks gestation with a positive one hour post-50 g glucose challenge (>135 mg/dL) and a three-hour 100 g blinded OGTT. Recruitment criteria included fasting glucose <95 mg/dL with two or more abnormal values post-glucose load. A total of 485 women meeting the inclusion criteria were randomized to treatment; however, no unified treatment protocol prevailed at all the treatment centers. The no-treatment arm consisted of 473 women receiving usual prenatal care. The treated subjects performed daily self-monitored blood glucose monitoring. Seven percent of the participants required insulin treatment to achieve glycemic control. The composite outcome consisted of perinatal death, neonatal hypoglycemia, hyperbilirubinemia, elevated cord C-peptide levels, and birth trauma.

There are several important distinctions among the studies. The inclusion criteria for the Langer and ACHOIS studies were higher than those in the MFMU study (fasting <95 mg/dL). Thus, only the first two studies represent the whole spectrum of glucose abnormality, whereas the third represents only the lower end of the glucose severity scale. Using only the lower end of the spectrum was considered potentially unethical to withhold treatment of women with elevated fasting glucose levels.[76] Moreover, studying patients at the lower end of the spectrum may result in masking the magnitude of complications leading to adverse outcome; it may also lead to erroneous conclusions. All the studies were powered to detect 30% difference in outcome parameters. However, treatment protocols differed among them from individualized counseling to a homogeneous standardized regimen. In addition, the definitions of composite outcome and metabolic complications (hypoglycemia, hyperbilirubinemia, etc.) as well as the ethnic mix of the populations were not comparable. Finally, criteria for NICU admission differed, confounding the use of NICU as a measure of neonatal morbidity (Figure 22-1). Each study has merits and provides valuable information to the GDM saga. However, it is more accurate to compare the first two studies[7,9] as the inclusion criteria are similar. The MFMU study can be compared to the segment in the Langer study of patients with fasting plasma glucose <95 mg/dL.[8] (Table 22-2). In addition, multiple logistic regression analysis confirmed fasting glucose as the most predictive factor for the composite perinatal outcome in untreated GDM. Controlling for maternal weight, parity, and disease severity according to fasting glucose level also revealed a two- to threefold decrease in adverse outcomes with treatment.

TABLE 22-2 The Rate of Adverse Outcome in Untreated Gestational Diabetes

	Pregnancy Outcome: In Untreated GDM		
	Langer AJOG 2005	Crowther NEJM 2005	Landon NEJM 2009
Composite (%)	59.0	4.0	37.0
Macrosomia (%)	17.0	21.0	14.3
LGA (%)	29.0	22.0	14.5
Ponderal index (%) (>2.85)	22.0	—	—
NICU admission (%)	24.0	61.0	11.6
Metabolic complication (%)	29.0	14.0	28.3
Respiratory complication (%)	12.0	4.0	2.9
Shoulder dystocia (%)	2.5	3.0	4.0
Stillbirth (/1000)	5.4	5.7	0.0
Cesarean section (%)	24.0	32.0	33.8
N	555	510	473

CAN TREATMENT OF GDM IMPROVE ADVERSE OUTCOME?

Is there any benefit to the increased surveillance and treatment initiated after a GDM diagnosis? It has been recognized and established by all authoritative bodies that glycemic control will enhance perinatal outcome and that poorly controlled and untreated GDM is associated with increased rates of macrosomia, stillbirth, and other neonatal complications.[77,78] The potential for successful treatment of diabetes in pregnancy including GDM will determine pregnancy outcome. Thus, failure to achieve successful outcome is not due to the questionable need for treatment but may suggest an inappropriate treatment approach.

In a randomized trial of treatment for GDM, Garner et al.[79] conducted a pilot study in Canada of "strict glycemic control" and tertiary care versus routine obstetric care in the management of women with normal fasting glucose levels (diet-controlled GDM). Among 300 GDM women studied, there were no differences in mean birth weight, macrosomia, or birth trauma. The mode of delivery was also similar between the two groups, whereas the treatment group did have lower preprandial and postprandial glucose levels during the third trimester. This feasibility study, however, reveals several areas of concern. The rate of macrosomia was 19% in the "untreated" and 16% in the treated group. These macrosomia rates are 40%–80% above the baseline rate reported in Canada for nondiabetic populations and raise the question of the quality of glycemic control in this study. The women in the control arm could have been "self-treating" by modifying their own diet on the basis of self-education. It is possible that the women in the control group received feedback from the results of home glucose monitoring with resultant behavioral changes. Garner's study suggests that intensive treatment of GDM may have little effect on birth weight, birth trauma, operative delivery, or neonatal metabolic disorders.

The authors,[74] in a prospective quasi-randomized study of 2461 GDM women, compared conventional (n = 1316) to intensified therapy (n = 1145). The two diabetic groups were compared to a nondiabetic control in a ratio of 2:1 selected in a randomized approach from our general population. The conventional therapy consisted of fasting plasma glucose and two-hour postprandial levels monitored on a weekly basis at clinic visits. In addition, patients were required to perform visualized but not verified self-monitoring blood glucose four times daily. The women in the intensified group were selected per memory reflectance meter availability and instructed to test blood glucose seven times daily with a memory reflectance meter to ascertain accurate and reliable blood glucose information. The study revealed (1) significant adverse outcome for LGA and macrosomia, metabolic and respiratory complications and shoulder dystocia rates when the conventional group was compared to the intensified therapy group (Table 22-3). (2) There was a higher rate of NICU admission and length of stay for the conventional group. (3) In regards to maternal complications, no significant differences were found in the rates of preeclampsia, chronic hypertension, or chorioamnionitis among the three groups; the perinatal outcome variables also included cesarean section rates. The above variables were all found to be comparable between the intensified and the nondiabetic controls. (4) Furthermore, logistic regression to evaluate the net effect of potential contributing variables to the rate of macrosomia revealed that only mean blood glucose, gestational age at delivery, previous macrosomia, and GDM were significant, while obesity, parity, and ethnicity were nonsignificant for the intensified group. This study demonstrated that neonatal macrosomia is related to the level of blood glucose and that when this factor is controlled, the maternal size has minimal to no effect on fetal size in women with GDM. Furthermore, the cesarean section rate in GDM is not automatically a self-fulfilling prophecy; it is probably affected by different management protocols practiced in different centers. Of note, conventional treated patients had similar pregnancy outcomes than untreated GDM women. Again, emphasizing the importance of treatment protocol (intensified therapy) that positively affects pregnancy outcome (Table 22-4).

TABLE 22-3 Intensified versus Conventional Management of GDM

	Conventional	Intensified	Control
Macrosomia (%)	13.6	7.01	8.1
Large-for-gestational age (%)	20.1	13.1	11.9
Metabolic complication (%)	13.3	3.1	2.9
Respiratory complication (%)	6.2	2.3	2.1
Shoulder dystocia (%)	1.4	0.4	8.7
perinatal mortality (PNM) (/1000)	6.0	15.0	14.0
Cesarean section (%)	22.0	15.0	14.0
N	1316	1145	4922

TABLE 22-4 Outcome: Untreated versus Conventional and Non-GDM

	Untreated	Conventional	Non-GDM
Macrosomia (%)	16.8	13.6	7.8
LGA (%)	29.4	20.1	11.3
Ponderal index (>2.85) (%)	21.7	19.8	12.6
Composite outcome (%)	59.0	47.8	11.4
Metabolic complication (%)	29.0	13.3	2.1
Respiratory complication (%)	12.0	6.2	3.0
Shoulder dystocia (%)	2.5	1.4	0.6
Stillbirth (/1000)	5.4	3.6	1.8
Cesarean section (%)	23.7	22.0	14.2
N	555	1145	1110

Coustan et al.[80,81] reported reduction in the frequency of macrosomia in offspring of mothers with GDM treated with insulin during pregnancy. Lower frequencies of operative delivery, traumatic delivery, and neonatal hypoglycemia were reported in the insulin-treated group. Persson et al.[81] randomly assigned 202 women with GDM to treatment with diet alone or diet plus insulin. A subgroup of the diet-treated patients (14%) received insulin treatment when targeted blood glucose levels were not achieved with diet alone. Frequency of macrosomia was relatively low and did not differ in the two groups; however, it was not specifically compared with subjects who achieved or failed to achieve desired levels of glycemic control.

Weiss et al.[82] used an unorthodox and more invasive approach to identify the need for treatment of GDM with insulin (all having similar OGTT values). Amniotic fluid insulin concentrations were measured at 28–32 weeks gestation in 88 GDM subjects. Nineteen subjects with high amniotic fluid insulin (designated class A/B) received therapy with multiple doses of short-acting exogenous insulin. Sixty-nine women with normal amniotic fluid insulin values (designated class A) were treated with diet alone. Macrosomia was found in 4 out of 51 (7.8%) control, in 11 of 69 (20.4%) class A, and in 1 of 19 (5.3%) class A/B insulin-treated subjects. Drexel et al.[83] reported their efforts to prevent perinatal morbidity in GDM by tight metabolic control. Insulin therapy was initiated without a trial of diet alone if one or more values during the OGTT was ≥200 mg/ dL. The therapeutic goals were capillary blood glucose concentration <130 mg/dL one hour after breakfast, absence of ketonuria and weight gain ≤1 kg/mo. When blood glucose concentration exceeded the acceptable range in diet-treated subjects, insulin treatment was initiated (lente, ≥12 U/day). Whereas insulin was used in most subjects, the frequency of macrosomia was not different in the intensely treated subjects with GDM (group 2) compared to the normal control group; the frequency of macrosomia in the group of GDM with limited treatment (group 3) was significantly higher than that in group 2. However, the frequency of nonphysiological modes of delivery and of neonatal morbidity did not differ among the three groups. In addition, obesity, an important confounding variable in several of the studies cited, was not a common feature in these subjects. The protocol used in this study suggests earlier diagnosis and treatment of GDM than is practiced in most centers.

The randomized study by O'Sullivan[84] demonstrated reduced macrosomia but not perinatal mortality from 13.1% to 4.3% in treated subjects. The enrollment criteria were fasting glucose ≥110 mg/ dL. More than 40 years later, three seminal works reaffirmed and expanded our knowledge that adverse outcome is associated with GDM and that appropriate treatment will positively affect outcome. In mild hyperglycemia[8] and the studies showing all spectrums of the disease,[7,9] the small differences in the rates of abnormality are attributable to different management protocols, definition of terms, and the social and legal pressures on the care

providers, that is, the difference in cesarean section and NICU admission rates (Table 22-5).

The rate of adverse outcome in pregnancy along the glucose severity spectrum is presented in Table 22-6 and Figure 22-3. Even GDM women within the mild hyperglycemic category (fasting <95 mg/dL) benefitted from medical intervention. However, the category of <95 mg/dL plasma glucose had significantly less composite outcome, macrosomia, and LGA than the higher categories of severity. In contrast, in the treated group, all severity categories had similar outcomes. Figure 22-2 Untreated GDM's outcome with FPG < 95 mg/dL.

Fasting plasma glucose is accepted as the gold standard for severity of diabetes. This is true in type 2 individuals and in GDM women. In an attempt to control for different GDM severity levels in the treated and untreated GDMs, we stratified the patients based on increases in fasting plasma glucose (10 mg increments) for each severity category. In the treated GDMs, similar perinatal outcome exists for all fasting severity categories reiterating the importance of achieving targeted levels of glycemic control. In contrast, in the untreated GDMs, significant morbidity was found in each fasting plasma category of severity (Figure 22-3 and Table 22-6). Logistic regression revealed in the untreated group that fasting plasma glucose (severity of disease) had a significant independent impact when every 10 mg increment increased the likelihood of adverse outcome (composite) by 15%; for each pound increase in obese patients, the likelihood of adverse outcome increased by 3%. For treated GDMs, parity was found to have a 6% increment for every child and obesity and weight gain had a negligible effect although both were found to be statistically significant (Table 22-6).

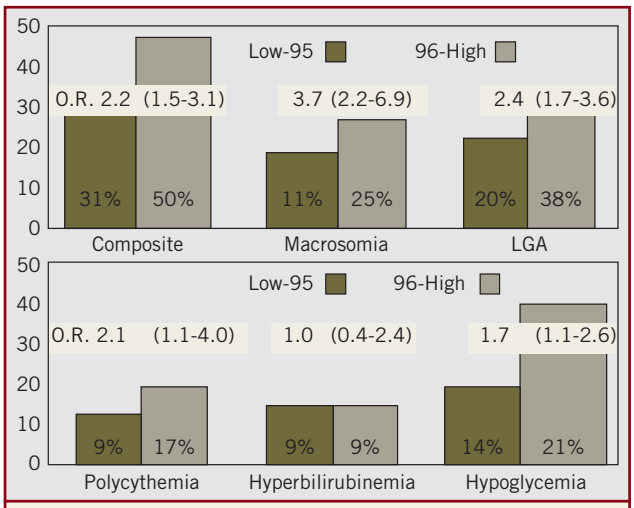

Figure 22-3 Outcome by disease severity (fasting plasma).

TABLE 22-5 Prevalence of Outcome in Treated Groups

	Langer AJOG 2005	Crowther NEJM 2005	Landon NEJM 2005
Macrosomia (%)	7.0	10.0	6.0
LGA (%)	10.7	13.0	7.0
Ponderal index (>2.85) (%)	13.8	—	—
NICU admission (%)	6.0	71.0	8.0
Metabolic complication (%)	10.0	16.0	—
Respiratory complication (%)	2.0	5.0	5.0
Shoulder dystocia (%)	0.9	1.0	—
Stillbirth (/1000)	3.6	0.0	—
Cesarean section (%)	23.2	31.0	31.0
Number of Patients	1110	490	490

TABLE 22-6 Prevalence of Perinatal Outcome by GDM Severity

Untreated vs. Well-Treated GDM (Mean 95 ± 7, Before Meal 89 ± 11, After Meal 104 ± 12)					
Fasting plasma glucose (FPG)	Low-95	96–105	106–115	116-HI	*P*
Untreated GDM					
Composite (%)	31	49	50	52	.0001
Marcrosomia (%)	11	26	21	22	.0001
LGA (%)	20	40	35	33	.0009
Well-treated					
Composite (%)	17	20	18	18	.65
Macrosomia (%)	7	8	7	5	.58
LGA (%)	10	13	11	7	.44

SUMMARY

Considering the metabolic heterogeneity of women with GDM and thus their likely broad range of perinatal risk, it is not surprising that descriptions of GDM have ranged from "a major health problem" to "a diagnosis still looking for a disease." We and others addressed the question of GDM as a clinical entity and the benefits of treating individuals with GDM that could have a significant impact on the provision of obstetrical care to pregnant women. GDM, when not treated, is associated with increased adverse outcome in pregnancy. Treatment and achievement of targeted levels of glycemic control will result in perinatal outcome comparable to that in the general population. Perinatal outcome and long-term complications for millions of mothers and their offspring are at stake. The time has come to cease the rhetoric and subdue the "tempest in a teacup." Tolstoy may have summed it up best:

> *I know that most men, including those at ease with problems of the greatest complexity, can seldom accept even the simplest and most obvious truth if it be such as would oblige them to admit the falsity of conclusions which they have delighted in explaining to colleagues, which they have proudly taught to others, and which they have woven, thread by thread, into the fabric of their lives.*

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Obesity in Pregnancy: A Sign of the Times?

23

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Only if we understand, will we care;
only if we care, can we help;
only if we help shall all be saved.

—Jane Goodall

Key Points

- Gestational diabetes and maternal obesity are independently associated with adverse maternal and neonatal outcomes with the largest net effect attributable to level of glycemia
- Prepregnancy counseling for severely overweight and obese gravids with diet and exercise interventions are recommended
- For obese women with body mass index (BMI) > 30 and gestational diabetes mellitus (GDM), achievement of targeted levels of glycemic control is associated with enhanced outcome when treated with pharmacological therapy (insulin or glyburide)
- Adverse perinatal outcome cannot be prevented in GDM obese women treated with diet therapy alone even with good glycemic control
- Treatment of obesity from diet to surgical intervention is not recommended during pregnancy
- Postnatal discussion at six weeks needs to include lifestyle changes to preclude future complications and the development of the metabolic syndrome

INTRODUCTION AND EPIDEMIOLOGY

The idea that there are obese people who are nonetheless healthy may be a myth. Although some overweight/obese people have normal elements of metabolic health, that is, normal cholesterol, glucose levels, and blood pressure, obesity by itself may increase the risk for serious diseases such as diabetes, heart disease, and death. Research over several decades has consistently demonstrated that obese pregnant women are at risk for adverse maternal, fetal, and neonatal outcomes.[1–3] Mounting epidemiologic evidence suggests that infants of obese mothers are at greater risk for lifelong metabolic complications that include diabetes mellitus, heart disease, and obesity through mechanisms of "in utero programming" of adult disease.[4,5] Obesity is also proving to be a significant contributor to the increased use of women's health care services and accompanying health care costs. It is difficult to ignore this increasing financial and resource burden of caring for obese patients during pregnancy and beyond. The practitioner of contemporary obstetrics needs no sophisticated statistics to alert him/her of the prevalence of obesity within the pregnant population and the complications and challenges they pose for both patient and care provider.[6–14]

Overweight and obesity are modern health epidemics; our current way of life is partially responsible for this disease. Both can be viewed as public health problems similar to the way dirty water was a problem about 100 years ago (*New York Times*, Friday, November 26, 2004). Obesity is a multifactorial phenomenon that consists of environmental, behavioral, genetic, and socioeconomic factors. It is also related to the imbalance of caloric intake versus expenditure. The factors that contribute to the achievement and maintenance of a healthy weight are essentially those acts and behaviors that can be considered a "healthy lifestyle." The consumption of less processed foods, fruits and vegetables, nuts and whole grains and low-fat protein sources, and the avoidance of refined sugar are all beneficial. Sustained physical activity, ideally on a daily basis is also important. The U.S. Surgeon General recommends at least 30 minutes of moderate physical activity daily.[15]

The clear but unfortunate trend toward a sedentary lifestyle and unhealthy eating habits has contributed to the so-called obesogenic state of U.S. society. This situation prevails despite the introduction and availability of dietetic, fat-free, low-fat, sugar-free and low-calorie foods and beverages, not to mention the pervasive presence of health clubs in most communities.

These nutritional disorders in the United States affect the majority of adults. Obesity has increased in every region of the United States, has affected both genders, and crosses all age groups, ethnicities, and education levels. There are more obese Americans today than at any previous time in our history. Although the number of obese Americans stood at just 13% in 1962, two-thirds of Americans are now classified as overweight or obese (62% of women). Since 1980, obesity rates have doubled for adults and tripled for children aged 12–19 years. This unfortunate "state of the weight" in the United States ultimately may undo the steady gains in overall health that Americans have enjoyed since the dawn of the 20th century.[6–8,16] The prevalence of obesity in adolescents has also increased, especially among Hispanic and African–American populations. The food industry deserves its share of the blame, especially in the United States and most recently in Europe. Eating out more often with lack of portion control and inappropriate food choices, especially from fast food establishments, have all contributed to the obesity epidemic.

PREVALENCE OF OBESITY

The growing prevalence of obesity, the metabolic syndrome, and type 2 diabetes in the United States has attracted the attention of scientists, the medical profession, policymakers, and the public. The metabolic syndrome is a combination of visceral obesity, atherogenic dyslipidemia (low levels of high-density lipoprotein [HDL], cholesterol, and elevated levels of triglycerides), hypertension, and glucose tolerance that contributes to insulin resistance and a heightened risk for diabetes and cardiovascular disease (CVD). The World Health Organization estimated in the year 2000 that as many as 300 million people worldwide were clinically obese. European countries are now following the health compromising trends found in the United States with as many as 30% of adults classified as overweight and obese.[17]

The prevalence of obesity is definition-dependent, that is, when normal body mass index (BMI) ranges from 18.5 to 24.9, 34% of the adult population is overweight. When you include obese adults (27%) with BMI $\geq$30, that number exceeds 60%.[16] The prevalence of obesity has increased by more than 75% since 1980[1] and the prevalence in children and adolescents has more than doubled since 1976.[2,3] Data from a nationally representative sample of 2630 English children showed that the frequency of overweight (>85th percentile) ranged from 22% at age 6 years to 31% at age 15 years and that of obesity (>95th percentile) ranged from 10% at age 6 years to 17% at age 15 years.[4]

Obesity rates also vary in different ethnic groups. In the United States, the prevalence of obesity among Afro-Americans and those of Hispanic origin is higher than that of Caucasians. Afro-Caribbean and Pakistanis living in the United Kingdom are more likely to be obese than the general population (OR 2.74 [95% CI 1.74–4.31], OR 1.71 [95% CI 1.06–2.76], respectively).[5] It has been suggested that these disturbing statistics may not be totally attributable to poor diet but also to a decline in total energy expenditure.[18] For example, young children are spending more time in sedentary activities (approximately 80%) versus vigorous physical activity (less than half hour/daily). This change in physical play may be one of the explanations for the increased rates of obesity and type 2 diabetes in children. Once virtually unheard of in adolescence, type 2 diabetes now accounts for approximately half of all new diagnoses of diabetes in some populations.[19] A retrospective cohort study of birth records linked to hospital discharge data for all live born singleton infants >37 weeks gestation (n = 312,412) born to African–American or Caucasian Missouri residents from 2000 to 2006 was conducted. Obesity was defined as prepregnancy BMI $\geq$ 30 kg/m^2. There were no differences in cesarean delivery or preeclampsia between obese African–American and Caucasian women. Infants of obese African–American women were significantly less likely to be macrosomic and more likely to be low birth weight compared to infants of obese Caucasian women. Compared to their normal-weight peers, obese Caucasian women had a greater relative risk of developing preeclampsia than obese African–American women.[20–22]

The epidemic rates of obesity and type 2 diabetes and their associated complications (e.g., hypertension, osteoarthritis) were the motivating factors for the establishment of guidelines by the National Institutes of Health (NIH) for weight loss both in obese and overweight persons.[23] Obesity-related morbidity may account for at least 6%–10% of health care costs in the United States.[24]

DEFINITIONS OF OBESITY

We need to exercise caution when analyzing data on obesity and pregnancy given the host of previously used calculations and definitions. Overweight and obesity are both terms for ranges of weight that are greater than what is generally considered healthy for a given height and, as such, have been associated with an increased likelihood for adverse health consequences.[23] Other methods of estimating body fat and body fat distribution include measurements of skinfold thickness and waist circumference, calculation of waist-to-hip circumference ratios, and imaging techniques such as ultrasound, computed tomography, and magnetic resonance imaging. The main stores for fat are subcutaneous and intra-abdominal; considerable amounts of fat can also reside within the muscles, especially in older adults. It is impossible to measure total fat in the body directly. The gold standard for estimating body fat has been hydrodensitometry (underwater weighing), which is based on the principle that fat tissue is less dense than muscle and bone. Other methods used in assessing the amount of body fat are body circumference (waist and hip), that is, 40 in for men and >35 in for women are considered high; skinfold thickness and bioimpedance. Measurements of skinfold thickness can provide reasonable assessment especially if taken at multiple sites. These measurements are subject to considerable variation between observers.[25,26] Measurement of bioimpedance is based on the principle that lean mass, because it is an electrolyte solution, conducts current better than fat mass. Therefore, measurement of the resistance to a weak current (impedance) applied across the extremities, when combined with height and weight and an empirically derived equation, provides an estimate of body fat.[27]

In clinical practice and epidemiological studies, body fat is commonly estimated by BMI, which is strongly correlated with fat mass measured densitometrically and adjusted for height; the correlation is 0.9.[25,26] BMI accounts not only for the subject's weight to define obesity but rather the relation between height

TABLE 23-1 Definition of Obesity

Category	BMI (kg/m^2)
Underweight	<18.5
Normal weight	18.5–24.9
Overweight	25–29.9
Obesity (Class I)	30–34.9
Obesity (Class II)	35–39.9
Obesity (Class III)	>40

World Health Organization. *Tech Rep Ser* 2000;894:1–4.

North American Association. *Study of Diabetes* 2000.

and weight. Several formulas have been devised to calculate this relationship. BMI is defined as weight in kilograms/the square of height in meters based on self-reported weight and height. The BMI can also be calculated as: (weight [lb] × 703)/(height [in]^2). To convert values of height to centimeters, multiply the height in inches by 2.54. To convert weight in pounds to kilograms, one must multiple by 0.45. It is a useful approximation of body fat, but it can often be misleading because muscular athletic individuals would most likely be considered overweight. A direct measurement of body fat may be more valid. Based on a NIH Consensus Development conference in 1985, obesity was defined as a BMI $\geq$27.8 in men and $\geq$27.3 in women.[28,29] The thresholds for normal weight, overweight, and obesity were modified and range from 18.5 to 25 for normal weight individuals, 26 to 29.9 over weight, $\geq$30 obese, and > 35 morbidly obese.[30] BMI is currently the most widely used measure to determine categories of bodyweight. An adult with a BMI ≥ 30 kg/m^2 is considered obese, although an individual with a BMI calculation between 25 and 29.9 kg/m^2 is considered overweight (Table 23-1).[30,31]

The literature on the influence of obesity on pregnancy outcome is hampered by a multitude of definitions of obesity. Some authors use maternal weight >200 lb at first prenatal visit under the assumption that only women with heights of 5'9" or more would be considered obese by BMI criteria and when the data on maternal height was not available.[32] Another approach is the use of the Metropolitan Life Insurance tables based on 50%–120% above the ideal weight as their criteria. Maternal obesity has been defined in various ways including a body weight above 80–114 kg (175–250 lb), a weight 50%–300% more than ideal prepregnancy weight (PPW) for height, and a maternal BMI from 26 to 29 (for overweight) or above 29 (for obesity).[33] The use of various definitions makes it difficult to compare results between studies if the populations are selected and classified based on varying criteria. In a way, this mirrors the dilemma in abstracting conclusions from studies of gestational diabetes mellitus (GDM) that use multiple criteria. However, regardless of the definition used, the adverse effects of excessive weight contribute to increased rates of perinatal mortality and morbidity.

PITFALLS IN BMI UTILIZATION

Again, if you cannot measure it, you cannot manage it. Unfortunately, many overweight and obese women are either not evaluated by their obstetrician for prepregnancy counseling or lack a documented PPW. The obstetrician must often rely solely on the patient to provide a recalled PPW that is then used to classify the patient as obese/nonobese, which will determine recommended gestational weight gain (GWG). Therefore, two pivotal questions remain: how accurate is reported PPW? And how many patients are inaccurately labeled based on self-reported values?

Overweight and obese women may underestimate self-reported PPW and overestimate GWG. Care providers' inability to know the actual prepregnancy weight of their patients may mistakenly categorize a patient's weight gain in pregnancy based on Institute of Medicine guidelines.[34] Rowland[35] performed a study regarding the validity and accuracy of individual's self-reported weight and height in a nonpregnant population. Heights and weights were self-reported during an interview and were then directly measured in a mobile examination site. Brunner[36] found comparable results when he evaluated women of reproductive age. The authors reported that women underestimated weight by 4.6 lb and overestimated height by 0.1 in. Self-reported weight and height measurements classified 84% of women into the appropriate BMI categories. Additionally, Brunner found that 81% of normal weight, 77% of overweight, and 90% of obese women were correctly allocated to the appropriate BMI category. The results in these studies were similar to the findings of Craig and Adams[37] who reported that although significant differences existed between self-reported and measured values, self-reported BMI categories still demonstrated moderate agreement. Stommel and Schoenborn[38] evaluated the accuracy of BMI based on self-reported height and weight using findings from National Health and Nutrition Examination Survey (NHANES) between 2001 and 2006. The authors found that self-reported and measured height and weight were highly correlated. Therefore, PPW as reported by the patient is a satisfactory substitute for clinical record data. Only underweight women over report weight by 2.4 lb.[39] There is a strong correlation between stated and actual PPW ($r = 0.98$).[40–44]

An accurate BMI can only be calculated using PPW. When an obstetrician uses weight in pregnancy, for example, weight at 24 weeks' gestation, he/she runs the risk of categorizing a nonobese woman as obese. In a randomized study, Szymansky and Satin[45] compared a measured PPW (22.3–24.2) and BMI calculated during the late second and early third trimesters (gestational age 25.9–30.7 weeks). The comparison revealed that all previous nonobese patients were now classified as overweight or obese (BMI 27.2–30.3). Failure to use PPW to classify BMI will result in masking the true weight category as well as over and under treatment of these patients.

THE INFLUENCE OF OBESITY ON PREGNANCY

Human pregnancy is an insulin-resistant condition. There is a 40%–50% increase in insulin resistance during pregnancy from the pregravid condition.[46,47] Alterations in insulin resistance have been linked to reproductive hormones such as human placental lactogen with more recent evidence suggesting that cytokines (TNG-α) may be a possible significant factor that modifies the insulin signaling pathway via serine phosphorylation of insulin receptor substrate-1, a primary substrate of insulin receptor.[48] Data on adipose cells have reported that it is a metabolically active tissue in addition to a storage depot for excess calories. Leptin and

cytokines have been reported to have paracrine as well as endocrine effects on many target tissues.[49] The risk for gestational diabetes is increased in the presence of obesity. Obesity is associated with hyperinsulinemia as is gestational diabetes.[50]

THE ASSOCIATION BETWEEN INFLAMMATION AND MICROVASCULAR FUNCTION

In the nonpregnant state, the effect of lipids, hyperinsulinemia, and obesity on vascular disease is mediated by an inflammation process. Arteriosclerosis is now considered a disease of inflammation[51] and serum concentrations of inflammatory markers have been demonstrated to be predictive of coronary events.[52] Adipose tissue secretes interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α). They inhibit insulin action at the adipocyte and at the level of the hepatocyte and skeletal muscle by altering insulin receptor function.[53] The inflammatory markers, C-reactive protein (CRP) and fibrinogen, derived from the liver under the influence of systemic cytokines, have been shown to be independent predictors of cardiovascular events.[54] The FRISC Study Group[55] and Cleland et al.[56] demonstrated that CRP concentrations, even within the normal range, strongly correlate with endothelial function as assessed by venous plethysmography in a group of healthy subjects. Regardless of the adjustment for CRP concentrations, IL-6 has been shown to be independently predictive of the risk for myocardial infarction.[57]

In the blood vessel wall, adhesion compounds (VCAM-I and lCAM-I) are produced. They are expressed and up regulated in response to stimulation by cytokines. In turn, circulating inflammatory cells affect the endothelium and are a step in the development of atheromatous deposits. Cytokines, soluble lCAM-I concentrations, and plasminogen (from adipose tissue) have all been found to be independent predictors and/or activators of coagulation pathways via the endothelium and circulating monocytes. Therefore, obesity is also associated with an elevated risk of venous thromboembolic disease.[58,59]

Additional hormones originating in adipose tissue are leptin (regulator of adipose tissue mass) and adiponectin.[60,61] Adiponectin levels are inversely related to visceral obesity and other cytokines (TNF-α).[62] Therefore, adipose tissue has been proposed as an active organ and not merely an inert storage for energy, with both autocrine and endocrine secretary function. They also influence liver and skeletal muscle that result in insulin resistance and dyslipidemia.

OBESITY AND THE DEVELOPMENT OF VASCULAR DISEASE IN PREGNANCY

The link between cardiovascular and metabolic risk in the nonpregnant state has been defined although there is paucity of information if these associations are relevant to adiposity in pregnancy. Sattar et al.[63] in a study of lean and obese pregnant women in the third trimester examined metabolic and inflammatory parameters and performed an in vivo assessment of endothelial-dependent and -independent microvascular function using laser Doppler imaging. Triglyceride levels were 22% higher and HDL concentrations 12% lower in the obese women; low-density lipoprotein (LDL) cholesterol and glycosylated hemoglobin were comparable for both groups. Leptin levels and fasting insulin were 150% and 123% higher, respectively. IL-6 and sensitive CRP were 50% and 100% greater in obese women than for lean women. CRP and insulin correlated inversely with the endothelial-dependent vasodilatory response. This data corroborate that obesity in pregnancy is associated with metabolic, inflammatory, and vascular risk factors that may add to maternal complications in obese women.[63]

Pregnancies compromised by preeclampsia are characterized by a twofold increase in triglyceride concentrations and a threefold increase in very-low-density lipoprotein (VLDL) and LDL-III concentrations in comparison to nonpreeclamptic subjects.[63] The changes as a result of hypertriglyceridemia may contribute to endothelial damage and insulin resistance. Preeclampsia is believed to be associated with an inflammatory state.[64]Granulocytes and monocytes release cytokines (TNF and IL-6) resulting in increased levels of cell adhesion compounds, VCAM-1 and ICAM-1. These metabolic and inflammatory stimuli induce microvascular dysfunction in preeclampsia and are proposed to arise from the placenta. The surplus inflammatory load that would occur as a result of obesity could potentially add fuel to this process, explaining at least in part the increased association of obesity with preeclampsia.

MATERNAL OUTLOOK

Obesity and Thromboembolic Disease

Pregnancy itself is a prothrombotic state with increases in the plasma concentration of coagulation factors I, VII, VIII, and X, a decrease in protein S and inhibition of fibrinolysis, resulting in a fivefold increased risk for venous thrombosis.[65,66] Other factors likely to be significant in the etiology of pregnancy-associated venous thromboembolism (VTE) are advanced maternal age, high parity, operative delivery, preeclampsia, and obesity. Abdollahi et al.[67] evaluated in a case-controlled study the risk of thrombosis because of overweight and obesity after a first episode of objectively diagnosed thrombosis. Obesity (BMI ≥30) increased the risk of thrombosis twofold. Obese individuals had higher levels of factor VIII and IX, but not of fibrinogen. In addition, the combined effect of obesity and oral contraceptive pills among women aged 15–45 revealed that pill users had a 10-fold increased risk for thrombosis when BMI was >25.

Hypertension Disorders

Hypertensive disorders have historically been associated with obesity in the pregnant and nonpregnant state. Authors have suggested a 10-fold higher rate of chronic hypertension in diabetic patients compared to normal-weight women.[68–72] The risk of pregnancy-induced hypertension or preeclampsia is significantly greater if the mother is overweight as assessed by BMI.[73,74] Studies suggest a two- to threefold increased risk for preeclampsia with a BMI >30. Sattar et al.[75] reported the results of the risk of hypertensive complications of pregnancy in association with a waist circumference of >80 cm in data from 1142 pregnant women. The risk of pregnancy-induced hypertension was twofold greater (OR 1.89% CI 1.1–2.9) and preeclampsia threefold (OR 2.7 95% CI 1.1–6.8) greater in association with visceral obesity. Waist circumference was demonstrated to be a more sensitive risk marker than BMI.[65–67]

In a study of 287,213 pregnancies, Sebire et al.[72] included 176,923 (61.6%) normal-weight (BMI 20–24.9), 79,014 (27.5%) moderately obese (BMI 25–29.9), and 31,276 (10.9%) very obese (BMI ≥ 30) women. Very obese women were two to three times more likely to develop proteinuric preeclampsia. Birth weight above the 90th percentile also increased in very obese women as was the incidence of intrauterine death. Intrapartum complications included an increased rate of induction of labor and caesarean section delivery. In the postpartum period, there was an increased rate of hemorrhage, genital tract infection, urinary tract infection, and wound infection. They concluded that maternal obesity carries significant risk for both mother and fetus with risk increasing with the degree of obesity and persists after accounting for other confounding demographic factors.

Bianco et al.[76] performed a retrospective cohort study of 613 morbidly obese (BMI > 35) and 11,313 nonobese women. A fourfold increased risk for preeclampsia was reported. There was a 50% increase in frequency of fetal distress and twofold increase in cesarean delivery. Postpartum, obese women had threefold increased incidence of endometritis. Kumari[68] evaluated 159 pregnant women with BMI > 40 and 300 women with normal BMI matched for age and parity. Women with preexisting diabetes and hypertension were excluded. Obesity was associated with hypertensive disorder of pregnancy in 28.8% of the obese compared to 2.9% in the nonobese group.

Epidemiological studies have shown a relationship between pregnancies complicated by preeclampsia and increased risk of maternal coronary heart disease in later life. The reported increase in the relative risk of death from ischemic heart disease in association with a history of preeclampsia/eclampsia is approximately twofold.[77] Preeclampsia shares many common pathological pathways with ischemic heart disease. The metabolic syndrome explains the influence of obesity on the development of hypertensive disorders and ischemic heart disease, dyslipidemia, and coagulation abnormalities.

OBESITY AND IMPLICATIONS FOR PREGNANCY OUTCOME

It is now universally acknowledged that maternal overweight and obesity are linked with adverse pregnancy outcome. Maternal complications include hypertension, diabetes, respiratory complications, (asthma and sleep apnea), thromboembolic disease, more frequent cesarean delivery with increased wound infection, endometritis, and anesthetic complications (mainly difficulties in intubation and placement of epidural). Newborn complications include large-for-gestational-age infants, stillbirths, shoulder dystocia, and long-term complications (obesity and diabetes). Morbidly obese women are prone to even more complications and adverse outcomes. A discussion of these complications should be the balance between the benefit/risk ratio of fetal and maternal perspectives.

OBESITY PREVALENCE AND PERINATAL RISK

More than 40% of pregnant women who are now initiating pregnancy are either overweight or obese.[78] Obesity complicates up to 28% of pregnancies, with 8% of women categorized as "extremely obese" based on a BMI of > 40 kg/m^2. In 1999, approximately 1 in 10 women weighed >250 lb; as many as 1 in 20 weighed >300 lb in a single prenatal population.[32] It is suspected that these numbers are even greater today. A multitude of maternal, fetal, neonatal, and potentially lifelong complications increase significantly when partnered with obesity. Greater risks for GDM, hypertensive disorders of pregnancy, fetal macrosomia, birth trauma, fetal malformations, protracted labor, operative vaginal delivery, shoulder dystocia, cesarean section (particularly emergent cesarean) delivery, and the postpartum complications of hemorrhage, thrombosis, and infection are all associated with obesity in pregnancy.[79–82]

Women who undergo cesarean section delivery run further risks of significant operative morbidity and death with greater blood loss, anesthesia complications, surgical technical difficulties, and complications of wound healing. These perinatal risks associated with maternal obesity stem from data obtained from a secondary analysis of a prospective cohort of >16,000 unselected patients in the United States.[83]

FETAL AND NEONATAL ISSUES

Perinatal Mortality

Perinatal mortality rates among offspring of obese patients are relatively low. Cnattingius et al.[84] presented data on over 167,000 women and suggested that prepregnancy obesity may not be a strong predictor for perinatal mortality as has been previously believed. This study reported an association between late intrauterine fetal death and higher prepregnancy BMI (OR 4.3 with a rate of 5–6/1000 in comparison to normal-weight women). They speculated that the hyperlipidemia of obesity may reduce prostacyclin secretion and enhance peroxidase production, resulting in vasoconstriction and platelet aggregation thus affecting placental perfusion. Baeten et al.[85] found that infant mortality was increased in the offspring of obese women but they did not report the rate. Sebire et al.[72] reported higher fetal death rates (OR 1.4 with a rate of 7/1000). In contrast, Kumari[68] and Bianco et al.[76] reported no increased perinatal mortality and fetal death in obese women after controlling for diabetes and hypertension. In modern obstetrics with appropriate fetal surveillance testing and the recognition of the potential at risk status of the fetus of the obese patient, the majority of perinatal mortality cases can be prevented, leaving macrosomia as the main concern for these neonates.

Abortion and Anomalies

A meta-analysis of 13 studies examined patient predictors for outcome of gonadotropin ovulation induction. The study revealed that the best predictors of poor outcome are obesity and insulin resistance. Obese patients were at threefold higher risk for spontaneous abortion in comparison to nonobese women (OR 3.05, 95% CI: 1.45–6.44).[86] A recent population-based study examined the association between overweight and obesity to several types of birth defects involving 40,000 births in a case-controlled study. The study demonstrated that obese women were approximately three times more likely than average-weight women to have an infant with either spinabifida or an omphalocele and about twice as likely to have a baby with either a heart defect or multiple anomalies, independent of intake of periconception multivitamins Table 23-2.[87–89]

TABLE 23-2 Obesity and Congenital Anomalies

	OR (95% CI)	
	Overweight	**Obesity**
Neural tube defects	1.2 (1.04–1.38)	11.87 (1.62–2.15)
Cardiovascular anomalies	1.17 (1.03–1.34)	1.3 (1.12–1.51)
Cleft lip and palate	1.0 (0.87–1.15)	1.2 (1.03–1.4) .02
Anorectal atresia	1.19 (0.91–1.54)	1.48 (1.12–1.97)
Craniosynostosis	1.24 (0.98–1.58)	1.18 (0.89–1.56)
Diaphragmatic hernia	0.95 (0.72–1.26)	1.28 (0.95–1.71)
Gastroschisis	0.83 (0.39–1.77)	0.17 (0.1–0.3)
Hydrocephaly	1.28 (0.93–1.75)	1.68 (1.19–2.36)
Hypospadias	1.13 (0.94–1.35)	1.08 (0.86–1.34)
Limb reduction	1.22 (0.97–1.53)	1.34 (1.03–1.73)
Microcephaly	1.21 (0.85–1.73)	1.10 (0.82–1.48)
Micro/anotia	0.97 (0.69–1.37)	1.11 (0.75–1.63)
Esophageal atresia	0.89 (0.66–1.21)	1.27 (0.60–2.67)

Source: Adapted from Gunatilake[88] and Stothard et al.[89]

Fetal Macrosomia

Many variables have been associated with fetal overgrowth or macrosomia. Increasingly, maternal pregravid weight and decreased pregravid insulin sensitivity have been shown to strongly correlate with fetal growth, especially fat mass at birth.[90] Increased maternal insulin resistance may be associated with altered placental function in addition to increased fetoplacental availability of nutrients in late gestation. These nutrients include not only glucose but also free fatty acids (FFAs) and amino acids. As a result, women with GDM may be at an increased risk of having a macrosomic infant; those who are obese with normal glucose tolerance are almost twice as likely to have a macrosomic infant.[91]

Maternal obesity is associated with an increased risk of fetal macrosomia (birth weight > 90th percentile [OR 2.36 95% CI 2.23–2.5]). Bergmann et al.[92] examined the Berlin Perinatal Registry for the period 1993–1999, which included data on 206,308 births. The incidence of a birth weight ≥4000 g increased significantly from 9.1% to 10.1% during this period. Possible contributing factors were examined and the group postulated that much of the increase in the frequency of macrosomic births could be attributed to increasing proportions of pregnant women older than 30, approximate 165 cm height, with a prepregnancy BMI of greater than 26 and a weight gain of more than 16 kg. In an adjusted multivariant analysis, a prepregnancy BMI of greater than 26 and a weight gain of greater than 16 kg were associated with a three- to fourfold increased likelihood of the delivery of a macrosomic infant. In addition, macrosomia was associated with a lower Apgar score and umbilical arterial pH, as well as severe injuries to the baby (injuries/fractures/palsies, OR 4.13 95 % CI 3.33–5.11) resulting in an overall morbidity of 8% with an increased rate of neonatal intensive care admission.[68,76]

Long-term Complications

Both the Barker[93,94] and fetal insulin hypotheses[95] have proposed that impaired adult cardiovascular health is programmed in utero by poor fetal nutrition, or by genetically determined reduction of insulin-mediated fetal growth that results in the birth of a small infant. Low birth weight may be a significant variable for the development of the metabolic syndrome in adulthood. Obesity was an independent risk factor in the diabetic populations studied. Therefore, the emphasis today may need to address sedentary lifestyle and issues related to obesity upon fetal programming because undernutrition is now infrequent in developed societies.

Another study[96] reported evidence of a link between maternal obesity and CVD in adult offspring, confirming Barker's hypothesis of higher adult death rates from coronary heart disease in men who were classified as low birth weight. In addition, they observed a positive association between the mother's BMI upon admission and future death rate from coronary heart disease in male offspring. They concluded that the mother's obesity may be an independent yet additional contributing factor to infant low birth weight. Fall et al.[97] reported higher adult rates of type 2 diabetes in offspring of mothers who were above average weight in pregnancy. Therefore, there is an association between maternal obesity (but not paternal) and insulin resistance on the risk of offspring to develop CVD in adulthood. In a further study, high maternal weight or BMI accounted for the association between birth weight and adult adiposity.[98]

Changes in maternal FFAs level may influence fetal programming. In a study supplementing fat in the diet of female rats prior to mating and throughout pregnancy, femoral artery responses to acetylcholine, as a marker of vascular endothelial dysfunction, were impaired in young adult offspring.[99] Cho et al.[100] reported an association between maternal second and third trimester FFA

concentrations (which increase with maternal obesity) and diastolic blood pressure in the adolescent offspring. The majority of evidence suggests a relationship between low birth weight and adult disease. However, it is reasonable to speculate that overweight infants who are a product of both genetic and environmental factors are programmed in utero for the development of future diabetes, obesity, and metabolic syndrome. Thus, diversity (accelerated and delayed) may be a source for adult disease already initiated in intrauterine life. Given that obesity and maternal insulin resistance are not only genetic but also acquired, improvement of preconception maternal insulin sensitivity via exercise or diet, and controlling the diabetes throughout pregnancy (improvement in intrauterine environment) may impact not only the mother's health but also the future cardiovascular risk for her child. Again, this hypothesis remains speculative and further research is needed to address this issue.

The Impact of Maternal Weight Gain in Pregnancy on Future Obesity

For decades, obstetricians associated maternal weight gain in pregnancy with deviant fetal growth. The amount of weight gain recommended in pregnancy is controversial. Historically, obstetricians used to restrict weight gain. Later on, a more lax approach to weight gain was the norm. In 1990, the Institute of Medicine published new guidelines based on the effects of weight gain on fetal size. The Institute stated that the effect of weight gain on fetal size diminishes as the mother's prepregnancy BMI increases.[101] The problem with this approach is that it was derived from the fetal perspective irrespective of the long-term effects on the mother. This concept was challenged in the past two decades when studies evaluated the association between maternal weight gain, obesity, pregnancy outcome, and future development of diabetes in the mother.

Rooney and Schauberger [102] evaluated the impact of excess pregnancy weight gain on development of obesity in late life. She studied a cohort of 540 women who had documented weight over a five-year postpartum period. She concluded that excess weight gain and failure to lose weight after pregnancy are important and identifiable predictors of long-term obesity. Breast-feeding and exercise may be beneficial in controlling long-term weight gain. Edwards et al.[103] evaluated 683 obese and 660 normal-weight women. Obese patients gained on average 11 lb less during pregnancy and were more likely to lose the weight or not gain weight at all. Obese women who lost or did not gain any weight had lower mean birth weights and higher rates of small-for-gestational-age infants in comparison to obese women who gained one pound or more in pregnancy. The incidence of macrosomic fetuses increased significantly only in the group that gained 12–16 kg (15.4%) and the group that gained more than 16 kg (24.4%). No weight gain and weight gain up to 11.5 kg were associated with a macrosomia rate of 12.5%–13.3% with a 10% rate in nonobese women. In light of the results, the authors recommend weight gains of 7–11.5 kg (15–25 lb) for obese women and 11.5–16 kg (25–35 lb) for normal-weight women to optimize fetal growth. Neonates of obese women who gained less than 15 lb were three times more likely to be small-for-gestational age than neonates of obese women who gained at least 15 lb.[104] In addition, it has also been reported that obese pregnant women who gained at least 15 lb demonstrated an increased frequency of macrosomia.[105]

Bianco et al.[76] reported that weight gain of more than 25 lb was strongly associated with birth of large-for-gestational-age infants. However, poor weight gain did not appear to increase the risk of low-birth-weight infants. Ratner et al.[106] examined the effects of weight gain on fetal outcome in obese women. Obesity was defined as 160% of ideal body weight. The percent weight gain varied from −18 to +64 lb. Fetal outcome was not different if mothers gained less or more than 10 lb. They concluded that limited weight gain in the morbid obese women does not adversely affect fetal outcome. Luke et al.[107] studied 487 term pregnancies that were stratified into underweight, normal weight, or over weight. They reported that for every kilogram of gestational weight gained, birth weight increased by 44.9 g for underweight women, 22.9 g for normal-weight women, and 11.9 g for overweight women. For every kilogram of retained weight, birth weight was increased by 35.6 g for underweight women, 15.9 g for normal-weight women, and 5.1 g for overweight women. These findings suggest that beyond a certain level of weight gain, there is an increase in birth weight at the expense of increasing maternal postpartum obesity for the woman who has gained an excessive amount of weight during pregnancy.

We[108] sought to determine the impact of maternal weight gain on fetal growth in gestational diabetes in relation to treatment modality, BMI, and glycemic control. Well-controlled was defined as glycemic control <100 mg/dL in 2454 GDM women. Overall, the results demonstrated a significant increase in large for gestational age (LGA) rates for different weight gain categories as defined by the Institute of Medicine (IOM) for obese and overweight compared to normal-weight subjects. The LGA/SGA (small for gestational age) rates were further modified by level of glycemic control and treatment modality. The key findings of the study revealed (1) 75% of the overall weight gain occurred prior to the GDM diagnosis; (2) stratification of GDM subjects by prepregnancy BMI categories identified thresholds that may limit excess LGA rates: for normal BMI ≤35 lb, overweight ≤15 lb, and obese ≤10 lb; and, for prevention of SGA in normal and overweight women ≥10 lb; (3) for obese subjects, there was no effect on the amount of weight gain category on the rate of SGA (4) in insulin treated nonobese patients, the rate of LGA increased only after a weight gain ≥40 lb and for overweight and obese women a weight gain ≥30 lb; (5) for insulin treated patients in good control, only those with a weight gain ≥36 lb demonstrated a significant increase in LGA; (6) with the inclusion of glycemic control, diet-treated subjects had significantly higher rates of LGA regardless of BMI and weight gain categories; (7) no association was found between SGA infants and level of glycemia, prepregnancy BMI category, and treatment modality.

Overall, studies of the association between pregnancy weight gain in obese women and neonatal size have been inconclusive with some reporting no or weak associations[104,106,109–111] and others reporting a strong association.[112–115] Studies supporting either position had limited length of follow-up except Rooney's study (five years); the majority of studies were cross-sectional design, which made it impossible to determine if postpartum maternal weight represented pregnancy weight retention, a regain of weight after an initial loss during gestation or a return to pregravid weight. Despite the limitations of existing studies and the continued controversy over recommendations for limited or unlimited weight gain during pregnancy in obese women, clinicians need to

continue to provide care with the knowledge and skills currently available. We now have improved assessment instruments available to determine fetal growth that also strengthens our ability to intervene in the interests of both the mother and child. Minimal maternal weight gain in obese women should not be considered a red flag of concern; rather, excessive weight gain should be a point of concern because of the implications for short- and long-term fetal and maternal morbidity and mortality.

LABOR COMPLICATIONS AND OBESITY

The obese woman in labor faces a greater likelihood of undergoing an operative vaginal delivery that is associated with higher maternal and fetal morbidity (1.5-fold in BMI >30 kg/m^2 and twofold in BMI > 40 kg/m^2).[116] Intrapartum risks of shoulder dystocia and birth trauma have also been reported as more likely in the obese patient carrying an appropriately grown or macrosomic fetus.[117] A study examining maternal anthropometric parameters that are associated with shoulder dystocia found that obesity is one of the strongest risk factors (2.7-fold risk) even after adjustment for confounding factors such as macrosomia and diabetes. Obesity predisposes to fetal macrosomia that, in addition to increasing the risk for shoulder dystocia and associated inherent birth trauma, contributes to perineal lacerations, fetal injury, and postpartum hemorrhage.[118]

An attempted operative vaginal delivery in an obese patient must be made judiciously with informed consent. Obesity also appears to contribute to the failure of medical induction of labor. In a secondary analysis of data obtained during a labor induction trial in which patients were stratified according to BMI, the median dose and duration of predelivery oxytocin was significantly greater among patients with a BMI of >40 kg/m^2 (5.0 units and 8.5 hours) versus their normal BMI counterparts (2.6 units and 6.5 hours). In another large prospective European series of >200,000 deliveries, a BMI greater than 40 kg/m^2 was associated with a four times risk of cesarean delivery because of failed or obstructed labor, despite attempts at augmentation.[119] These studies highlight the greater inherent risks of failed induction of labor in this patient population. Even when labor occurs spontaneously, it is less likely to progress according to standard labor curves for the obese parturient. In a prospective study of 509 nulliparous patients who underwent labor induction in a standardized fashion as maternal weight increased, the rate of cervical dilation decreased and the induction to delivery interval lengthened.[120] Similar findings that indicated a slower rate of labor progress in the active phase were observed for overweight and obese women. After adjustment for factors that included labor induction, membrane rupture, oxytocin use, epidural analgesia, GWG, and fetal size, the median duration of labor from 4 to 10 cm was significantly longer for both overweight and obese women, compared with normal-weight women (7.5, 7.9, and 6.2 hours, respectively).[121]

We have historically sought the answers to the mechanism of uterine contractility and with this information to understand premature labor, labor abnormalities, and so forth. Essentially, excitation is the electrochemical event that occurs at the membrane level and is followed by the mechanical event, that is, contraction. First, there is depolarization of the plasma membrane that causes activation of voltage-activated Ca^{2+} channels allowing an influx of calcium. Calcium binds to calmodulin and together they form a complex that activates myosin light chain kinase. In turn, myosin light chain kinase phosphorylates the myosin light chain that forms cross bridges with actin. The cycling of these cross bridges is the molecular mechanism for contraction. The smooth muscle fibers of the uterus are connected by gap junctions that act as low-resistance pathways for the rapid spread of electrical signals throughout the tissue. The fibers contract essentially in unison. The biochemical mechanisms underlying dysfunctional labor with obesity are largely unknown. However, in vitro studies of uterine myometrium that were obtained from obese women at the time of cesarean section delivery demonstrate impaired contractility.[122] There is also the suggestion that leptin, which is released by adipose tissue, may inhibit uterine contractions.[123]

Since the early 1960s, attempts have been made to relate uterine activity to electrical myometrial myography in rats and rabbits.[124–126] Studies showing that propagation of the myometrial electrical activity is facilitated by gap junctions that quantitatively increase prior to the onset of labor were followed up by noninvasive recordings of uterine electromyographic signals (EMG) from the abdominal surface in human subjects.[127–130] The majority of these studies included women at term and used two sets of electrodes without a position sensor. We used an innovative approach that measured electric uterine activity in the smooth muscle of the uterus.[131] The objectives of our study were to utilize noninvasive transabdominal electrical uterine myographic measures. Our approach for monitoring electric uterine muscle (EUM) was defined as electrical activity of the uterine muscle measured in units representing the peak mean of the electrical activity (root mean square [RMS]).We used nine electrodes evenly spaced on the patient's abdomen to optimize the signal to noise ratio. Although previous EMG studies were conducted without a position sensor, this novel approach with EUM-100 applies both multichannel surface EMG and a three-dimensional position sensor that enables mapping of each electrode's location within 1 mm. This represents an accurate localization of the myometrial activity of the uterus in three dimensions. We found that patients with false or premature labor can be identified by measuring uterine electrical activity. In another study,[132] using the above methodology, we found that obese patients had lower electric uterine activity. In this study of 84 patients who met our initial study criteria, we obtained 144 electromyography measurements that were then compared to BMI information. All electromyography testing was done with the EUM-100 machine that has been described elsewhere. Comparing underweight and normal-weight women, and overweight and obese, there was no significant difference in each group in electric uterine activity. However, comparing normal weight to overweight and obese, there is a statistically significant difference, *P* value of .0026. Our data suggest a negative association between BMI and electrical uterine activity. This difference was most notable between normal-weight subjects (and below) and overweight or obese individuals. These findings support the copious retrospective data showing an increased risk of cesarean delivery with increasing BMI. Additionally, the data provide evidence of the causal relationship between obesity, labor progression abnormalities, and cesarean delivery, that is, decreased uterine electrical activity. This may be the result of the dyslipidemia associated with obesity and its effect on the cell membrane functionality of the myometrium.

Vahratian et al.[121] studied labor progression in overweight and obese women. He compared the median duration of labor for each centimeter of dilatation: for normal-weight women approximately 6.2 hours to progress from 4 to 10 cm; overweight women 7.52 hours; and, obese women 7.94 hours. These differences were statistically significant. Upon further analysis, the authors were able to show that the majority of the difference in labor curve for overweight versus Normal-weight women occurred between 4 and 6 cm, whereas in obese women the difference persisted throughout the first stage of labor. No differences were observed in the length of second stage of labor for normal-weight versus overweight versus obese women.

Zhang et al.[122] studied the association between obesity and poor labor progression and subsequent increased risk for cesarean delivery. They focused on the relationship between BMI and hypercholesterolemia and the possible role that cholesterol plays in controlling smooth muscle contractility. BMI and dyslipidemia are known to be positively associated. Cholesterol-rich regions of the cell membrane termed lipid rafts and caveolae are important for signal transduction and receptor mediation. Abnormalities in lipid milieu have been shown to modulate smooth muscle contractility. Chu et al.[81] published a meta-analysis of the numerous studies on this association. Of the 127 papers that addressed obesity and pregnancy complications, 33 were included to specifically scrutinize the relationship between obesity and cesarean section. The analysis revealed: overweight versus normal OR 1.46 95% CI 1.34–1.60, obese 2.06 1.86–2.27, and, severely obese 2.89 2.28–3.79.

Studies have also focused on the possibility that a decrease in uterine contractility may be a major contributor to increased labor abnormalities and cesarean delivery. Our findings support the numerous retrospective data demonstrating increased risk of labor abnormalities and cesarean delivery associated with maternal overweight and obesity. Further, our data highlight a possible cause—poor myometrial contractility. Our research has demonstrated a negative linear correlation between BMI and electrical uterine activity with statistically significant differences detected in the electrical activity of the myometrium of normal-weight versus overweight and obese individuals. This decrease in electrical uterine activity is reflective of a decrease in depolarization of the smooth muscle of the uterus. Data from multiple studies have consistently shown an increased likelihood for either an elective or emergent cesarean section delivery with obesity. This risk relationship appears to have a positive correlation not only with prepregnancy BMI but also with excessive GWG.[72,133–134]

The higher risk for cesarean section delivery is particularly worrisome given the greater inherent perioperative risks of surgery, which are further magnified in the obese population. Cesarean delivery in this population also complicates the management of subsequent pregnancies and creates ongoing cumulative obstetric risk issues that are related to uterine rupture, placenta previa, placenta accreta (and its variances), and perioperative morbidity that includes operative injury, hemorrhage, intensive care unit admission, and the need for transfusion. In a large-scale study of over one million women from the Swedish Medical Birth Registry, women were categorized into six classes of BMI. Obese women were compared with normal-weight women regarding adverse neonatal outcome after suitable adjustments. Four modes of delivery were evaluated: vaginal delivery, instrumental vaginal delivery, elective cesarean delivery, and emergency cesarean delivery. Neonates born to morbidly obese women were at markedly increased risk of adverse neonatal outcome regardless of mode of delivery.[135]

We sought to determine whether pregnancy outcome differs between obese and morbidly obese GDM patients and to assess pregnancy outcome in association with mode of treatment and level of glycemic control. A cohort study of 4830 patients with gestational diabetes, treated in the same center using the same diabetic protocol, was performed. Obesity was defined as prepregnancy BMI > 30 and <35 kg/m^2; morbid obesity was defined as prepregnancy BMI > 35 kg/m^2. Well-controlled GDM was defined as mean blood glucose < 105 mg/dL. Pregnancy outcome measures included the rates of large-for-gestational-age and macrosomic babies, metabolic complications, need for neonatal intensive care unit (NICU) admission and/or respiratory support, rate of shoulder dystocia, and the rate of cesarean section. Among the GDM patients, the rates of obesity and morbid obesity were 15.7% (760 out of 4830, BMI: 32.4 $\pm$ 1.6 kg/m^2) and 11.6% (559 out of 4830, BMI: 42.6 $\pm$ 2.2 kg/m^2), respectively. No differences were found with regard to maternal age, ethnicity, and gestational age at delivery or oral glucose tolerance test (OGTT) severity. Moreover, similar rates of cesarean section, fetal macrosomia, shoulder dystocia, composite outcome, and metabolic complications were noted. Insulin treatment was initiated for 62% of the obese and 73% of the morbidly obese GDM patients ($P < .002$). Similar rates of obese and morbidly obese patients achieved desired levels of glycemic control (63% vs. 61%, respectively). In both obese and morbidly obese patients who achieved a desired level of glycemic control (<105 mg/dL), no difference was found in pregnancy outcome except that both neonatal metabolic complications and composite outcomes were more prevalent in diet treated versus insulin-treated GDM patients. In obese women with GDM, pregnancy outcome is compromised regardless of the level of obesity or treatment modality.[136]

In general, there is scant data on the association and mechanism responsible for the influence of obesity on labor.[137,138] Jensen et al.[137] in a large study found that overweight and obesity (BMI definition) are only weak predictors of labor complications in normal pregnancy. They found significantly more primary inertia for the overweight and obese groups and secondary inertia only in the obese group resulting in higher rates of oxytocin augmentation in these patients. In addition, they found higher rates of cephalopelvic disproportion (CPD) in patients with BMI > 25. Garbaciak et al.[139] found obese women at increased risk for delivering by cesarean section even without evidence of labor complications. Similar findings were described by Rasmussen,[140,141] which included higher rates of induction but no negative effects of obesity on labor. Data from a large private practice were used to examine factors associated with caesarean section delivery. A significant relationship was found between maternal BMI > 30 and the rate of delivery by caesarean section following a diagnosis of CPO and failure to progress (OR 6.5 95% CI 6.2–6.9 after correction for gestational age and birth weight). This figure persisted despite adjustment for maternal demographic confounders (OR 9.25 95% CI 8.5–9.9). The authors attributed increased soft tissue obstruction of labor as a potential contributor.[119]

A multicenter study demonstrated that vaginal delivery of patients with prior cesarean section is associated with increased morbidity for the mother.[142] Obese patients have higher rates of complications during and following cesarean delivery such as deep vein thrombosis, pulmonary embolism, infections, wound separation, and so forth. However, there is scant data on the management of subsequent pregnancies among obese women with at least one prior cesarean delivery. Chauban et al.[143] studied 69 patients weighing 300 lb or more who had prior cesarean delivery. Fifty-seven percent of the study population underwent elective repeat delivery; 43% attempted trial of labor with only 13% delivering vaginally. The main reason for failure to achieve vaginal delivery included arrest disorder in 46%, fetal distress in 38%, and failed induction in 15% of cases. The results of this study raise the question of the benefits of trial of labor in morbidly obese patients because there is an increased risk of infection and other major complications. However, regardless of circumstances, cesarean section delivery rates today are influenced not only by medical necessity but also by local politics, as much as by women who a prior demand a cesarean delivery.

THE ASSOCIATION BETWEEN MATERNAL OBESITY AND GDM

The association between obesity, hypertension, and insulin resistance in type 2 diabetes is well recognized. It has been shown that even minor degrees of carbohydrate intolerance are related to obesity and pregnancy outcome.[144,145] Jensen et al.[145,146146] evaluated pregnancy outcome and BMI in glucose-tolerant nondiabetic Danish women. They concluded that the risk of hypertensive complications, cesarean section, induction of labor, and macrosomia was significantly increased in both overweight women (BMI 25.0–29.9) and obese women (BMI ≥30.0) compared with women of normal weight (BMI 18.5–24.9). The frequencies of shoulder dystocia, preterm delivery, and infant morbidity other than macrosomia were not significantly associated with maternal BMI. Prepregnancy overweight and obesity were associated with adverse pregnancy outcome in glucose-tolerant women. Sebire et al.[72] found a twofold increase in the rate of GDM (OR 1.68, 95% CI 1.53–1.84). Kumari[68] comparing obese and nonobese found a 24.5% rate of GDM for the obese and 2.2% for nonobese subjects. Bianco et al.[76] reported a threefold increase in GDM for obese patients.

We[147] in a study of 6857 women, the majority of whom were Mexican–American, found a direct association between glucose screening categories, obesity, and rate of GDM. For patients with screening results from 130 to 189 mg/dL, the rate of obesity was approximately 24%–30%. Thereafter, this rate increased twofold. In contrast, for nonobese women, the rate of GDM increased for each 10 mg increment in glucose screening. This data demonstrates that the rate of obesity and glucose tolerance is both associated with the development of GDM. Additionally, we[148] demonstrated that fetal size and cesarean section rates are associated with the degree of carbohydrate intolerance as represented by screening results. Furthermore, obesity remains a significant contributor impacting fetal size.

Nondiabetic pregnant women have been the populations in the majority of studies that addressed the relationship between maternal PPW and perinatal outcome.[68,72,76,85,119,144–146,149–158] However, there is less data on obesity and overweight in gestational diabetes. Leiken et al.[159] demonstrated an independent risk for macrosomia among obese GDM women. They determined that gestational diabetes had a frequency of macrosomia no different than that of nondiabetic subjects. Nonobese GDM women with fasting hyperglycemia treated with diet and insulin therapy also had a frequency of macrosomia no different than that of nondiabetic women. However, diet and insulin did not prevent excess macrosomia in women who were obese. These studies had small sample sizes, failed to provide information on glycemic control and only evaluated single outcome variables. Maternal age, parity, and obesity are all overrepresented among GDM women. These variables need to be controlled in a study to draw accurate conclusions that also control confounding effects. Therefore, it is not clear if obesity, level of glycemia, or treatment modalities is independently or cumulatively responsible for fetal growth abnormalities.

We found[160,161] that obese and overweight GDM patients achieving established levels of glucose control with insulin therapy showed no increased risk for composite outcome, and macrosomia and LGA in comparison to normal-weight GDM patients. In contrast, even when diet treated obese patients achieved good glycemic control, there was no improvement in pregnancy outcome in comparison to normal-weight patients. Poorly controlled overweight and obese patients, regardless of treatment modality, had significantly higher rates of composite outcome, metabolic complications, macrosomia, and LGA. Although obesity in and of itself portends potential adverse outcome in pregnancy, gestational diabetic women treated with insulin and possibly oral antidiabetic drugs who achieve targeted levels of glycemic control will have pregnancy outcomes comparable to those of normal-weight women. The improved outcome in the insulin treated overweight and obese women may be because of an unidentified effect of insulin itself on the fetus or activation of other metabolic fuel pathways Tables 23-3 and 23-4.

Several studies have suggested a higher rate of morbidity in morbidly obese nondiabetic pregnant women. We found no significant difference between obese and morbidly obese women in pregnancy outcome compromised by diabetes when targeted levels of glycemic control were achieved. However, two-thirds of the morbidly obese patients failed to achieve the desired level of glycemic control and 69% were treated with insulin. In a multiple logistic regression analysis, we controlled for the potential effect of unaccounted factors on perinatal outcome. In addition to constitutional risk factors such as previous macrosomia and parity, level of glycemic control, obesity, and treatment modality were found to be independent contributors to the outcome variable. These findings support the premise that treatment with insulin and achievement of established levels of glycemic control in obese patients will result in enhanced pregnancy outcome. In our study, for obese patients treated with diet, there was a twofold higher risk for cesarean delivery when compared to overweight and normal-weight subjects. For the insulin-treated group, regardless of BMI category and achievement of targeted levels of glycemic control, there were similar rates of cesarean section. The overall cesarean section rate for diet was 23% and for insulin subjects 27%.

Insulin resistance and hyperinsulinemia are hallmarks of GDM and obesity. It is also a common finding in individuals with dyslipidemia and hypertension. Approximately half of all patients with essential hypertension both lean and obese are resistant to insulin

TABLE 23-3 Bivariate (Unadjusted) Analysis of the Impact of Overweight and Obesity on Pregnancy Outcome in 1307 Well-Controlled Diet-Treated Patients

	BMI (kg/m²)	No. Affected	% Affected	OR vs. 18.5–24.9 kg/m²	95% CI
Metabolic complications	18.5–24.9	80	6.1	1	—
	25–29.9	88	6.7	1.10	0.65–1.88
	>30	140	10.7	1.84*	1.02–3.32
Composite outcome	18.5–24.9	214	16.4	1	—
	25–29.9	314	24.0	1.61	1.17–2.21
	>30	356	27.2	1.90*	1.36–2.66
Macrosomia	18.5–24.9	73	5.6	1	—
	25–29.9	111	8.5	1.56	0.95–2.56
	>30	187	14.3	2.79*	1.74–4.46
LGA	18.5–24.9	144	11.0	1	—
	25–29.9	264	20.2	2.03*	1.38–2.90
	>30	273	20.9	2.10*	1.27–2.75
Preeclampsia	18.5–24.9	98	7.5	1	—
	25–29.9	105	8	1.06	0.50–2.23
	>30	139	10.6	1.45	0.63–3.33
Chronic hypertension	18.5–24.9	182	13.9	1	—
	25–29.9	294	22.5	1.80*	1.11–2.91
	>30	362	27.7	2.37*	1.45–3.86
Overall C/S	18.5–24.9	208	15.9	1	—
	25–29.9	246	18.8	1.22	0.86–1.73
	>30	399	30.5	2.31*	1.56–3.43

*$P < .05$.

and the insulin resistance resides primarily in muscle and involves the glycogen synthetic pathways.[46,47] The majority of studies have found an association between hypertensive disorders and obesity in nondiabetic pregnant subjects. Our studies[160,161] confirmed the association of increased chronic hypertension rates with maternal BMI. The incidence of chronic hypertension was not influenced by level of glycemic control or treatment modality. Regardless of achieving established levels of glycemic control, the rate of preeclampsia was not significantly different between diet-treated overweight and obese subjects. The relatively low rate of GDM severity in diet-treated patients (fasting plasma glucose < 95 mg/dL) may account for this difference. In insulin-treated subjects, an approximate threefold higher risk for preeclampsia was found in the patients who failed to achieve established levels of glycemic control. Insulin-treated patients in all BMI categories who achieved established levels of glycemic control had similar rates of preeclampsia.

IS IT OBESITY, GDM OR BOTH THAT INFLUENCE ADVERSE PERINATAL OUTCOME?

Gestational diabetes and maternal obesity are independently associated with adverse maternal and neonatal outcomes.[162] Both share common metabolic characteristics such as increased insulin resistance, hyperglycemia, and hyperinsulinemia. Just as GDM may impart distinct effects on perinatal outcomes independent of obesity, so does maternal obesity. Therefore, examination of the combined association of these common metabolic problems with pregnancy outcomes is an important question. Catalano et al. sought to determine the association between gestational diabetes and obesity in relation to adverse outcome in pregnancy. They concluded that both maternal GDM and obesity are independently associated with adverse pregnancy outcomes. Their combination has a greater impact than either one alone. Relative to non-GDM and nonobese women, OR for birth weight at 90th percentile for GDM alone was 2.19 (1.93, 2.47), for obesity alone 1.73 (1.50, 2.00), and for both GDM and obesity 3.62 (3.04, 4.32). However, similar results were found for primary cesarean delivery, preeclampsia, cord C-peptide, and newborn percent body fat.[163] These investigators concluded that maternal obesity has a strong independent relationship with adverse perinatal outcome.[164,165]

The knowledge that GDM and obesity independently influence adverse perinatal outcome predisposed the advancement of the term "diabesity." However, the net effect of each contributor to the magnitude of adverse outcome such as metabolic and

TABLE 23-4 Bivariate (Unadjusted) Analysis of the Impact of Overweight and Obesity on Pregnancy Outcome in 1069 Well-Controlled Insulin-Treated Patients

	BMI (kg/m²)	No. Affected	% Affected	OR vs. 18.5–24.9 kg/m²	95% CI
Metabolic complications	18.5–24.9	58	5.4	1	—
	25–29.9	103	9.6	1.87*	1.01–3.46
	>30	120	11.2	1.99*	1.11–3.57
Composite outcome	18.5–24.9	155	14.5	1	—
	25–29.9	212	19.9	1.47	0.97–2.23
	>30	214	20.0	1.47	0.99–2.17
Macrosomia	18.5–24.9	56	5.2	1	—
	25–29.9	75	7.0	1.36	0.71–2.60
	>30	92	8.6	1.71	0.94–3.10
LGA	18.5–24.9	78	7.3	1	—
	25–29.9	108	10.1	1.27	0.78–2.06
	>30	96	9.0	1.69*	0.90–2.62
Preeclampsia	18.5–24.9	67	6.3	1	—
	25–29.9	94	8.8	1.44	0.56–3.72
	>30	115	10.8	1.81	0.78–4.20
Chronic hypertension	18.5–24.9	175	16.4	1	
	25–29.9	280	26.2	1.81*	1.03–3.27
	>30	376	35.2	2.76*	1.62–4.70
Overall C/S	18.5–24.9	258	24.1	1	
	25–29.9	235	22.0	1.12	0.76–1.66
	>30	277	25.9	1.10	0.77–1.56

*$P < .05$.

respiratory complications has minimally been assessed. Therefore, we examined our data from a previous study of untreated GDM.[166] Untreated GDM were stratified into three groups: obese, overweight, and normal subjects. They were matched to non-GDM subjects based on the following variables: obesity, ethnicity, gestational age at delivery, number of prenatal visits, and parity. The nondiabetic subjects were assigned to three mutually exclusive groups: nonobese, overweight, and obese. Comparison within each BMI weight category revealed that untreated GDM in all weight categories demonstrated a 2- to 10-fold higher risk for composite outcome, LGA, metabolic and respiratory complications, shoulder dystocia, preeclampsia, induction of labor and cesarean section delivery. Moreover, when lean untreated GDM (BMI 18.5–24.9) were compared to obese nondiabetic subjects for adverse pregnancy outcomes, no difference was shown. The only exception was a higher rate (two- to fivefold) for induction of labor and cesarean delivery. The higher rate of cesarean delivery and induction of labor on obese patients suggests that this increased risk is the result of physicians employing the self-fulfilling prophecy when obese patients are about to deliver. Moreover, our data demonstrated that even lean untreated GDM (mainly abnormal glucose) have comparable outcomes to obese nondiabetic women. The data suggest the enhanced magnitude of unregulated glucose as a major contributor to adverse outcome in pregnancy.

THE IMPLICATIONS OF OBESITY AND POSSIBLE INTERVENTIONS

For many women, a gynecologist is the only health care provider that she will see during her lifetime. Therefore, it is incumbent on this care provider to incorporate whole person care that will include not only issues of reproduction and gynecology but also issues related to the newest practices in lifestyle management as well as pharmacological and surgical therapy for obesity.[167]

The Nonpregnant Population

It is now well established that obesity and particularly a central body fat distribution correlate strongly with deviant metabolic function and are associated with an increased rate for the development ofCVD.[168–170] Many of the risk factors are modifiable, and totally or partially preventable. Data from the Nurses Health Study[171] suggested that women who retain a desirable body weight, eat a healthy diet, and exercise regularly (in addition to smoking cessation/avoidance and moderate alcohol consumption)

can reduce the risk of CVD by 84%. Because only 3% of the women studied actually followed these recommendations, there is need for more public awareness through education and the media on the implementation of preventive strategies for both the current and future cohorts to deter risk factors.

Lifestyle Interventions

An intensive lifestyle intervention designed for weight loss failed to reduce the risk of cardiovascular events after a decade for overweight/obese patients with type 2 diabetes when compared with an intensive educational and support program. The lifestyle intervention reduced the risk for developing kidney disease and depression with lower medical expenditures. Observational studies of the effects of weight loss in these two groups produced conflicting results.[172] The study was prematurely halted after a maximum 11-year follow-up because of the futility to find a difference between groups on cardiovascular complications. In a Cochrane Review[173] authors independently assessed the risk of bias and extracted data on the effect of weight loss in hypertensive patients. This Review critically assessed the literature on whether dietary intervention for weight loss is an effective therapy for reducing hypertension among obese men and women. They concluded that it is not known whether weight loss precludes mortality and morbidity for this population.

The major environmental factors that increase the risk of type 2 diabetes are over nutrition and a sedentary lifestyle, with consequent overweight and obesity. Not surprisingly, interventions that reverse or improve these factors have been demonstrated to have a beneficial effect on control of glycemia in established type 2 diabetes. Unfortunately, the high rate of weight regain has limited the role of lifestyle interventions as an effective means of controlling glycemia in the long term. The most convincing long-term data indicating that weight loss effectively lowers glycemia have been generated in the follow-up of type 2 diabetic patients who have had bariatric surgery. In this setting, with a mean sustained weight loss of >20 kg, diabetes is virtually eliminated.[174–176] In addition to the beneficial effects of weight loss on glycemia, weight loss and exercise improve coincident CVD risk factors, such as blood pressure and atherogenic lipid profiles, and ameliorate other consequences of obesity.[177] There are few adverse consequences of such lifestyle interventions other than difficulty in incorporating them into usual lifestyle and sustaining them and the usually minor musculoskeletal injuries and potential problems associated with neuropathy. Theoretically, effective weight loss, with its accompanying benefits, safety profile, and low cost, should be the most cost-effective means of controlling diabetes—if it could be achieved and maintained over the long term. Given these beneficial effects, which are usually seen rapidly—within weeks to months—and often before there has been substantial weight loss, a lifestyle intervention program to promote weight loss and increase activity levels should, with rare exceptions, be included as part of diabetes management. Weight loss of as little as 4 kg will often ameliorate hyperglycemia. However, the limited long-term success of lifestyle programs to maintain glycemic goals in patients with type 2 diabetes suggests that the large majority of patients will require the addition of medications over the course of their diabetes.

Abdominal fat has been proposed as a source of FFA and cytokine production both of which promotes vascular inflammation and endothelial dysfunction, potentially resulting in insulin resistance and hypertension. One can speculate that either a reduction in BMI or redistribution of body fat may improve both the inflammatory profile and insulin sensitivity that will reduce the risk of CVD. Interventional studies demonstrated that weight loss over one year was associated with a reduction in inflammatory cytokine concentrations, lowering of adhesion molecule concentrations, including ICAM-1 and an improvement in endothelial dependent vascular function.[178] In a randomized study of lifestyle change or drug therapy in women with elevated fasting and postload plasma glucose levels, the study showed that lifestyle modification including exercise and weight loss was more effective than treatment with metformin in reducing the progression to type 2 diabetes.[179] However, the limited long-term success of lifestyle programs to maintain glycemic goals in patients with obese and type 2 diabetes suggests that the majority of patients will require the addition of medications over the course of their life. Obesity also contributes to higher rates of some cancers. The American Cancer Society study found in a prospective design a relationship between BMI at baseline and deaths from cancer during a 16-year follow-up. They concluded that there is a positive association between excess body weight and death because of most cancers.[180]

Statins

Cholesterol-lowering statins are widely used as part of the management for obese and diabetic patients. One of the common side effects of the use of statins is muscle cramping. This condition can be remediated with the use of comparable statins within the drug group and/or dose titration. A British group of physicians (CTT group) published a meta-analysis of 26 randomized trials involving more than 169,000 participants. They found that reducing LDL cholesterol from 38 to 77mg/dL via statins reduces the risk of vascular events such as heart attack, coronary revascularization, and stroke by approximately 40%–50%.[181] In 2012, another CTT meta-analysis was published in *The Lancet* of 27 randomized trials involving over 174,000 patients. This analysis revealed that even low-risk patients who would not normally be considered for statin therapy derive as much risk reduction for vascular events from statins as high-risk patients do.[182] In 2012, the Food and Drug Administration (FDA) announced labeling changes to cholesterol-lowering statins to include warnings about diabetes risk and memory loss. This warning was motivated from existing data from the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. The study noted a 27% increase in investigator-reported diabetes in patients who took rosuvastatin compared to a placebo.[183] A consideration when pharmacological therapy is administered is the risk/benefit ratio. No doubt that developing diabetes is not a desired outcome, but having a heart attack or stroke and dying is even worse. Statin labeling now includes a warning that cognitive effects such as memory loss and confusion have been reported in people taking the drugs. The FDA based its warning on reports to its Adverse Event Reporting System (AERS). In contrast, in a recently published study, it was reported that memory loss occurred in only 0.06% of participants, or less than 1 in 1000.[184] Awareness of potential side effects is important but throwing out the baby with the bath water will deny patients the potential for maximizing health benefits.

Bariatric Surgery and Pregnancy

Bariatric surgery is considered the most effective method for weight loss for the severely obese patient.[185,186] Bariatric surgery can be divided into two main categories: malabsorptive procedures (jejunoileal bypass, biliopancreatic diversion, and the duodenal switch) and restrictive procedures (banded and ringed vertical gastroplasty and gastric banding). All of these operations can be performed either by open surgery or aparoscopically.[187] In Europe, as well as other countries worldwide, laparoscopic adjustable gastric banding (LAGB) is the most popular restrictive bariatric operation. More than 100,000 patients by 2006 had undergone this type of surgery.[188,189]

Recently, the American Diabetes Association (ADA) published a bariatric surgery position statement:[190]

Bariatric surgery may be considered for adults with BMI 35 kg/m^2 and type 2 diabetes, especially if diabetes or associated comorbidities are difficult to control with lifestyle and pharmacological therapy. Patients with type 2 diabetes who have undergone bariatric surgery need lifelong lifestyle support and medical monitoring. Although small trials have shown glycemic benefit of bariatric surgery in patients with type 2 diabetes and BMI 30–35 kg/m^2, there is currently insufficient evidence to generally recommend surgery in patients with BMI <35 kg/m^2 outside of a research protocol. The long-term benefits, cost effectiveness and risks of bariatric surgery in individuals with type 2 diabetes should be studied in well-designed controlled trials with optimal medical and lifestyle therapy as the comparator. Bariatric and metabolic surgeries, either gastric banding or procedures that involve bypassing, transposing, or resecting sections of the small intestine, when part of a comprehensive team approach, can be an effective weight loss treatment for severe obesity, and national guidelines support its consideration for people with type 2 diabetes who have BMI exceeding 35 kg/m^2.

Advantages

Bariatric surgery has been shown to lead to near- or complete normalization of glycemia in 40–95% of patients with type 2 diabetes, depending on the study and the surgical procedure. A meta-analysis of bariatric surgery studies involving 3,188 patients with diabetes reported that 78% had remission of diabetes (normalization of blood glucose levels in the absence of medications) and that the remission rates were sustained in studies that had follow-up exceeding 2 years. Remission rates tend to be lower with procedures that only constrict the stomach and higher with those that bypass portions of the small intestine. Additionally, intestinal bypass procedures may have glycemic effects that are independent of their effects on weight, perhaps involving the incretin axis. There is also evidence for diabetes remission following bariatric surgery in persons with type 2 diabetes who are less severely obese. One randomized trial compared adjustable gastric banding or procedures that involve bypassing, transposing, or resecting sections of the small intestine, when part of a comprehensive team approach, can be an effective weight loss treatment for severe obesity, and national guidelines support its consideration for people with type 2 diabetes who have BMI exceeding 35 kg/m^2.Overall, 73% of surgically treated patients achieved "remission" of their diabetes, compared with 13% of those treated medically. The latter group lost only 1.7% of body weight, suggesting that their therapy was not optimal. Overall the trial had 60 subjects, and only 13 had a BMI under 35 kg/m^2, making it difficult to generalize these results widely to diabetic patients who are less severely obese or with longer duration of diabetes. In a recent nonrandomized study of 66 people with BMI 30–35 kg/m^2, 88% of participants had remission of their type 2 diabetes up to 6 years after surgery.

Disadvantages

Bariatric surgery is costly in the short term and has associated risks. Morbidity and mortality rates directly related to the surgery have been reduced considerably in recent years, with 30-day mortality rates now 0.28%, similar to those of laparoscopic cholecystectomy[191] Longer-term concerns include vitamin and mineral deficiencies, osteoporosis, and rare but often severe hypoglycemia from insulin hypersecretion. Cohort studies attempting to match subjects suggest that the procedure may reduce longer term mortality rates. Retrospective analyses and modeling studies suggest that these procedures may be cost-effective for patients with type 2 diabetes, when one considers reduction in subsequent health care costs.[192–195] Caution about the benefits of bariatric surgery is warranted. A propensity score-adjusted analysis of older severely obese patients with high baseline mortality in Veterans Affairs Medical Centers found that bariatric surgery was not associated with decreased mortality compared with usual care (mean follow-up 6.7 years). A study that followed patients who had undergone laparoscopic adjustable gastric banding (LAGB) for 12 years found that 60% were satisfied with the procedure. Nearly one out of three patients experienced band erosion, and almost half had required removal of their bands. The authors' conclusion was that "LAGB appears to result in relatively poor long-term outcomes". Understanding the mechanisms of glycemic improvement, long-term benefits, and risks of bariatric surgery in individuals with type 2 diabetes, especially those who are not severely obese, will require well designed clinical trials, with optimal

medical and lifestyle therapy, and cardiovascular risk factors as the comparator.[196–204]

Referral for bariatric surgical consultation is appropriate for women with a BMI ≥ 40 kg/m^2 or for those women whose BMI is > 35 kg/m^2 when comorbid conditions (such as diabetes mellitus, coronary artery disease, or severe sleep apnea) are present.[205] Patients who undergo bariatric surgery procedures to achieve weight loss generally demonstrate overall recovery in quality-of-life measures and improvement or resolution of medical comorbidities. Bariatric surgical patients who achieve modest weight reductions have also shown improved pregnancy outcomes, with reductions in pre-GDM, preeclampsia and large-for-gestational-age infants.[206–208] The best results are achieved typically when bariatric surgery is followed by healthful lifestyle modifications.[209] In general, patients should be counseled to avoid pregnancy for at least 12–18 months after the procedure because of a higher risk for surgical complications and avoidance of exposure of the fetus to the rapid weight-loss phase after surgery.[205] However, recent evidence suggests that outcomes may be similar before the 18-month window.[210,211]

Reviews of pregnancy treatment among patients with previous bariatric surgery have been published.[205,212] In anticipation of a pregnancy, patients require the obstetric provider to query operative reports or surgical consultants to determine the exact procedure that was performed. There should be ongoing surveillance for gastrointestinal complications because malabsorptive bariatric procedures (e.g., Roux-en-Y bypass) have been associated with bowel obstruction, stricture, and nutritional deficiencies (B_{12}, folate, iron) in pregnancy. In contrast, complications that relate to port infection, gastric band migration, and gastric perforation have been reported after restrictive bariatric procedures (e.g., laparoscopic adjustable gastric band placement and laparoscopic sleeve gastrectomy).[205,206] Maternal deaths have also been reported.[213] Patients should be advised on vitamin supplementation with B_{12} and at least 400 mg of folic acid to prevent nutritional deficiencies in pregnancy. Four high-protein meals are preferred over six meals daily.[205] If significant nausea and vomiting are experienced in pregnancy with an adjustable gastric band, the band should be adjusted to improve gastric emptying.[214]

Treatment Options

Approximately 73% of the population describe themselves as trying to lose weight.[215] Studies have shown that only about 20% of obese adults can lose approximately 2 lb/wk by decreasing daily intake from 500 to 1000 kcal below the caloric intake required for the maintenance of their current weight.[216] Diets that are lower in caloric intake may increase the rapidity of weight loss but not the long-term sustained weight loss success rate.[23] The innumerable weight loss diets are testimony to the lack of effectiveness of any one approach. Exercise may be the component that provides the long-term maintenance of the weight loss. Persons who embark on a weight loss/exercise program can expect to lose 5%–10% of preintervention body weight over a four- to six-month period. Although they perceive it as minimal weight loss, it may suffice to improve many obesity-related conditions.[217]

Improvements, however, are not sustained if weight is regained; slow weight gain to often preintervention levels happens for the majority of persons. Losing the weight is often the easier part; long-term maintenance of reduced weight is even more challenging.[218] Bariatric surgical treatment can induce long-term weight loss. It involves not only shrinking the size of the stomach, but also rearranging the small intestines to control how many calories can be absorbed. A patient will feel full, to the point of pain, after only a small amount of food, roughly 2 oz. Because patients eat so little, fewer than 1200 cal/d, they need to take vitamin and mineral supplements for the rest of their lives. In addition, the surgery is expensive, costing more than $40,000. This procedure is appropriate only for persons with BMI 40 or a BMI of 35 with accompanying obesity-related medical conditions.[23] The newer stomach-reduction procedure, called adjustable gastric banding is considered safer although weight loss is more gradual. There are possible complications with the band. Although the risk of death is much lower than with gastric bypass surgery, the band can slip up or down, which requires that it be reset; it also requires periodic tightening. There is currently no good scientific evidence of which procedure is best. Weight loss surgery in appropriate patients can lead to long-term weight loss, less diabetes, and a lower death rate.

In pregnancy, previous bariatric surgery was not associated with adverse perinatal outcome.[219] This confirms the results of studies by Martin et al. and others concluding that women who conceived soon after the procedure had uncomplicated pregnancies.[220–223] However, these pregnancies were found to be associated with an increased risk of anemia because of vitamin deficiencies.[224]

When nonpharmacological regimens have not substantially reduced the medical risks, weight-loss medications may be useful adjuncts to behavior modification. The NIH Guidelines suggest that nonpharmacological regimens be attempted for six months if unsatisfactory weight loss (less than one pound/month) persists. Prescription medications can help carefully selected obese patients lose weight and can preclude the rate of regain. Drug therapy in combination with behavior modification may provide the best results.[225]

The history of treatment of hypertension in many ways mirrors the current state of treatment for obesity. Few medications were available and their efficacy was limited but continuous research efforts into the underlying causes and consequences of hypertension have made dramatic strides. A comparable research effort in the understanding of obesity may likely have comparable results in being able to help obese persons achieve and maintain a healthy weight and lifestyle. It is mandatory that obesity be addressed as a chronic condition that requires continuous medical attention and care. To alter the obesity epidemic, strategies and programs for weight loss and maintenance must become a higher public health priority. Treatment of obesity from diet to surgical intervention is not recommended during pregnancy. The main effort for these patients is to address obesity during preconception.

Pregnant Population

In obese women, a modification of risk factors prior to or early in pregnancy is recommended. Treatment options during pregnancy using diet, pharmacological or surgical means are contraindicated in comparison to those in the nonpregnant state. Statins are category X (contraindicated for use in pregnancy) and should be

TABLE 23-5 Clinical Suggestions for Management of the Obese Gravid

- Prepregnancy counseling for overweight and obese gravids in pregnancy-related complications, especially diabetes and hypertension
- Educating patient on lifestyle changes such as healthy diet and exercise and avoiding excessive weight gain
- Consider detailed anomaly scan
- For obese and morbidly obese, glucose tolerance testing at first office visit and if negative, repeat at 28 wk
- Insulin or glyburide for obese GDM is recommended
- Obtain anesthesia consult prior to labor and delivery
- Anticipate labor complications (i.e., shoulder dystocia) to allow optimum management with experienced professional present
- In light of high infection rate, consider prophylaxis if prolonged labor or complicated delivery
- Postnatal review at 6 wk to discuss any problems and potential for future intervention such as bariatric surgery

discontinued before conception, as should angiotensin converting enzyme (ACE) inhibitors.[226] angiotensin receptor blockers (ARB)s are category C (risk cannot be ruled out) in the first trimester but category D (positive evidence of risk) in later pregnancy and should generally be discontinued before pregnancy. Because many pregnancies are unplanned, health care professionals caring for any woman of childbearing age should consider the potential risks and benefits of medications that are contraindicated in pregnancy. Among the oral antidiabetic agents, metformin and acarbose are classified as category B (no evidence of risk in humans) and all others as category C. Potential risks and benefits of oral antidiabetic agents in the preconception period must be carefully weighed, recognizing that there is paucity of data and the FDA categorization is not up to date. Planned pregnancies greatly facilitate preconception diabetes care. Unfortunately, nearly two-thirds of pregnancies in women with diabetes are unplanned, potentially leading to fetal malformations. A recent study showed that preconception counseling using simple educational tools enabled adolescent girls to make well-informed decisions lasting up to nine months.[227] Lack of preconception care (PCC) was associated with a major increase in poor pregnancy outcome because only 17% of obstetric units delivered multidisciplinary PCC, whereas others delivered care from general diabetes clinics. This resulted in prepregnancy counseling for type 1 diabetes, 39% and type 2 diabetes, 25% ($P < .05$). Use of folic acid supplements with pregestational diabetes: type 1, 43% and type 2, 29% ($P < .05$). Finally, HbA1c < 7% in first trimester for type 1 was 35% and for type 2, 49% ($P < .05$). Discussion regarding the use of contraception accounted for 32%.[228–230]

SUMMARY

Obesity has implications for all aspects of maternal health and outcome during pregnancy. Improved lifestyle changes can mitigate pregnancy complications. Health professionals and social service providers need to actively promote a healthy lifestyle at every opportunity to their patients and clients. Prepregnancy clinics could provide education on healthy diet and exercise regimes similar to those provided for women with diabetes. Managed care in the United States does not currently focus on preventative measures for either mother or child. Improvement of health prospects for the mother during pregnancy and the potential risk for developing complications later in life should begin early and be the focus of care. A concerted effort by public policy makers and the medical community could also effectively reduce health care costs, including those for hospitalization resulting from hypertensive disease, fetal anomalies, fetal assessment, costs associated with the high rate of caesarean section, and postpartum complications (Table 23-5).

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The Metabolic Syndrome and Long-Term Implications for the Mother

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Truth always lags last, limping along the arm of time

–Baltasar Gracian

Key Points

- The metabolic syndrome (MS) is a cluster of clinical and metabolic factors linked by resistance to insulin action and associated with an increased risk of cardiovascular disease (CVD), type 2 diabetes, and several other diseases
- Gestational diabetes mellitus (GDM) has many features of MS including a predisposition to developing type 2 diabetes and the presence of risk factors for CVD
- Identification of MS is important so that intervention with lifestyle modification or pharmacotherapy can be initiated to prevent progression to these illnesses

INTRODUCTION

Cardiovascular disease (CVD) is the commonest cause of death and disability in women in the United States (US).[1] In 2009, CVD accounted for 25% of all-cause mortality in women.[1,2] Another serious illness, type 2 diabetes mellitus, is also very common, occurring in approximately 12.6 million or 10.8% of all women aged 20 years or older.[3] About one-third of women are unaware of their diagnosis.[3] As many as one in three U.S. adults could have diabetes by 2050 if current trends continue.[4] Individuals diagnosed as having type 2 diabetes have large reductions in life expectancy. In 2003, it was estimated that women diagnosed after age 40 in the United States would lose 14.3 life-years and 22.0 quality-adjusted life-years.[5] More recently, in 2012, it was reported from Canada that diabetes in women was associated with a loss of life expectancy and health-adjusted life expectancy of 6 years and 5.8 years, respectively.[6] Much of this increase in mortality and morbidity is because of an increase in CVD, which is the most common complication attributable to diabetes. The risk for CVD is more serious among women than men. The relative risk for fatal coronary heart disease in women with diabetes is 1.5 that of men. This increased risk may be because of more cardiovascular risk factors in women and disparities in health care that favor men.[7] Mortality rates for heart disease are reported to be increasing for women although they have declined for men since the 1980s and recently surpassed those for men.[8] Young women, in particular, have shown the greatest rise in coronary deaths and this is reported to be related to an increase in cardiac risk factors including diabetes and the metabolic syndrome (MS).[9]

Multifactorial risk factor reduction is effective for the primary and secondary prevention of CVD.[10–12] Similarly, it has been shown that the progression to type 2 diabetes in at-risk individuals can be significantly delayed or even prevented by early lifestyle and pharmacological intervention.[13] Risk factors for CVD and type 2 diabetes tend to cluster together. This clustering of clinical and biochemical abnormalities has been termed "MS."[14] Gestational diabetes mellitus (GDM) can be considered a manifestation of the MS in pregnancy.[15] Identification of women with the MS or GDM provides an important opportunity to identify individuals at high risk for CVD and type 2 diabetes and to initiate preventive therapy. In this chapter, we will review the clinical significance of the MS in women, its relationship to GDM, and a clinical approach to identification and management.

PART 1: SCIENTIFIC BACKGROUND

Definitions

In 1988, Reaven proposed that resistance to insulin-stimulated glucose uptake (insulin resistance, IR) and secondary hyperinsulinemia are involved in the etiology of three major related diseases:

CVD, type 2 diabetes, and hypertension. He coined the term "Syndrome X" to describe a group of abnormalities that increase the risk for CVD: resistance to insulin-stimulated glucose uptake, glucose intolerance, hyperinsulinemia, increased triglyceride (TG), decreased high-density lipoprotein-cholesterol (HDL-C), and hypertension.[15] Since then, it has become widely recognized that cardiovascular risk factors tend to cluster although whether resistance to insulin action is central to this "syndrome" is controversial.[16] Several different names and diagnostic criteria have been proposed, including Insulin Resistance Syndrome, Dysmetabolic Syndrome, Deadly Quartet, and MS. The list of biochemical and clinical features included in the cluster has increased since its first description (Figure 24-1).[16]

Formal criteria for the diagnosis of the MS have been proposed to assist clinicians to identify patients at high risk of CVD and for study purposes (Table 24-1).[16,17] In the United States, the most widely used formal definition for the MS is that developed by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III.[14] The World Health Organization (WHO) also formulated diagnostic criteria with similar goals. The main difference is the inclusion of a measure of IR if glucose intolerance or type 2 diabetes is not present in clinical blood glucose measurements, and measurement of the urinary albumin excretion rate.[17] A small increase in urinary albumin excretion termed microalbuminuria is a predictor of increased risk of renal failure and CVD.[18] Use of morning urine albumin-to-creatinine ratio is

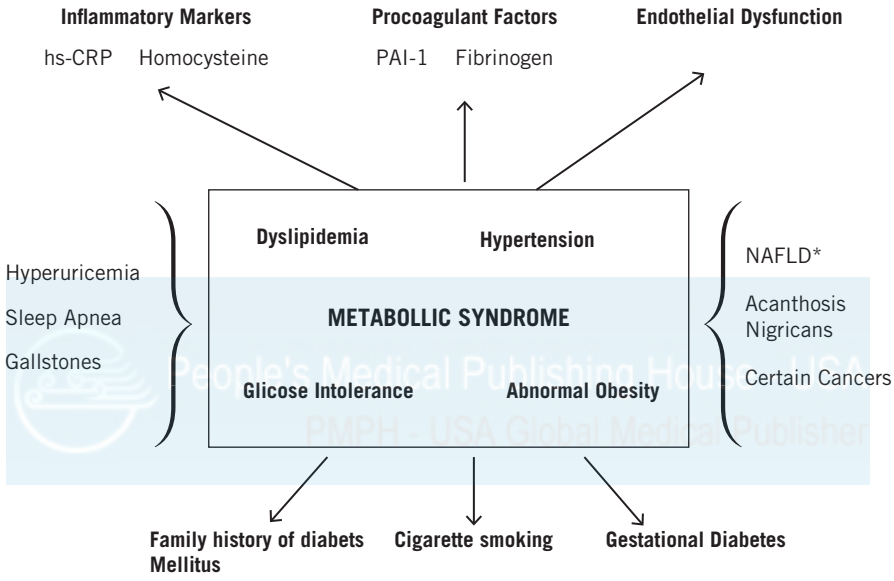

Figure 24-1 Cluster of biochemical and clinical abnormalities associated with the metabolic syndrome and insulin resistance.

TABLE 24-1 Comparison of NCEP ATP III and WHO Criteria for the Diagnosis of the Metabolic Syndrome

ATP III definition
Any three or more of the following criteria:
- Waist circumference > 102 cm in men and >88 cm in women
- Serum triglycerides > 1.7 mmol/L
- Blood pressure > 130/85 mmHg
- HDL cholesterol < 1 mmol/L in men and <1.3 mmol/L in women
- Serum glucose > 6.1 mmol/L (>5.6 mmol/L may be applicable)

WHO definition
Diabetes, IFG, IGT, or insulin resistance (assessed by clamp studies) and at least two of the following criteria:
- Waist-to-hip ratio > 0.90 in men and >85 in women
- Serum triglycerides > 1.7 mmol/L or HDL cholesterol < 0.9 mmol/L in men and <1.0 mmol/L in women
- Blood pressure > 140/90 mmHg
- Urinary albumin excretion rate > 20 μg/min or albumin-to-creatinine ratio > 30 mg/g

the preferred screening method. Fever, exercise, heart failure, and poor glycemic control can cause transient microalbuminuria.[19] In clinical practice, serum insulin measurements are not recommended because of lack of standardization of insulin assays.

Clinical Value of the MS

Although the ATP III criteria for the MS have been promoted as a means of identifying individuals at risk for type 2 diabetes and CVD, some studies have shown that other established risk scores (the Framingham Risk Score and the Diabetes Predicting Model) are superior for this purpose.[16] The Framingham Risk Score contains other well-recognized cardiovascular risk factors, not included in the NCEP ATP-III and WHO criteria, namely age, sex, total cholesterol (TC), and cigarette smoking. A high score predicts coronary events within 10 years. Similarly, family history, an important predictor of type 2 diabetes, is included in the Diabetes Predicting Model. It has been suggested that the current definitions of the MS are probably best as a "simple public health concept and an easily identified starting point for clinical interventions known to reduce risk for the increasing problems of type 2 diabetes, CVD, and perhaps some cancers."[20]

Prevalence of the MS in the United States

Data suggests the prevalence of the MS in the United States remains high but may be decreasing. The National Health and Nutrition Examination Survey (NHANES) showed age-adjusted prevalence of MS decreased from 26% to 23% from 1999 to 2010. There were, however, a difference in trends in the components of the syndrome with hypertriglyceridemia and hypertension each decreasing from approximately 34% to 24% in association with increased use of drug therapy for these disorders, whereas hyperglycemia increased from 13% to 20% and elevated waist circumference from 45% to 56%. Women, particularly nonwhite women, had the highest increase in prevalence of abdominal obesity.[21]

Cruz et al.[22] studied 126 Latino children living in Los Angeles. Inclusion criteria were age 8–13 years, a family history of type 2 diabetes, and overweight. The MS was defined as the presence three or more of the following: abdominal obesity, low HDL, hypertriglyceridemia, hypertension, and/or impaired glucose tolerance (IGT). The presence of 0, 1, 2, 3 or more features of the MS was 9%, 22%, 38%, and 30%, respectively. The incidence was higher in children of mothers with a history of GDM. In another study of U.S. children and adolescents, MS was present in 39% of 438 overweight, and in 50% of obese children, whereas none was found in normal-weight children.[23]

Risk Factors for the MS

Efforts have been made to identify pathophysiological precursors to the MS but no single unifying cause has been identified.[16] Obesity is the most important risk factor for the MS. In NHANES III, MS was present in 4.6%, 22.4%, and 59.6% of normal-weight, overweight, and obese men, respectively, and a similar distribution was observed in women.[24] Not all patients with increased IR are obese, however, and a subset of individuals termed "metabolically obese but normal weight" (MONW) has been identified. These individuals, despite having a normal body mass index (BMI) have an increased waist circumference and metabolic characteristics of the MS.[25] Conversely, not all overweight and obese individuals are metabolically unhealthy, but metabolically healthy obesity (MHO) may transition to metabolically unhealthy obesity.[26] Accumulating data suggest dysfunctional subcutaneous adipose tissue may underlie much of MS by promoting a proinflammatory state and IR[27,28] and markers of inflammation, such as serum levels of high-sensitivity C-reactive protein (hs-CRP) and homocysteine are also predictors of type 2 diabetes and cardiovascular events.[29,30] Birth weight is a risk factor for the MS and type 2 diabetes with both high and low birth weight increasing the risk of childhood and adult obesity.[31] The "thrifty-phenotype hypothesis" proposes that the survival of the undernourished fetus leads to adaptations in intrauterine developmental programming that ultimately result in IR.[31,32]

MS and Type 2 Diabetes and Cardiovascular Risk

There is undoubtedly a strong association between the MS and the risk for subsequent development of type 2 diabetes as demonstrated in numerous studies.[33] This however can be explained by the inclusion of abnormalities in glucose tolerance as a diagnostic criterion of the MS[16] and identification of the MS does not improve predictive value for diabetes. The Diabetes Predicting Model is reported to be superior to the MS in this regard.[34] Similarly, while there is a strong association between MS and cardiovascular risk, other models, notably the Framingham Risk Score are reported to be better predictors of CVS risk.[33,34]

MS and Other Conditions

The MS has also been associated with several other disorders including obstructive sleep apnea[35] and several cancers.[36] Obesity is proposed to mediate cancer through several mechanisms including IR and inflammation.[37]

Nonalcoholic fatty liver disease (NAFLD) is now the most common liver disease in the United States, with an overall prevalence of about 5% in the general population and between 25% and 75% in patients with obesity and type 2 diabetes. Nonalcoholic steatohepatitis (NASH) is predicted to become the commonest cause for liver transplantation in the United States between 2020 and 2030.[38] NASH occurs most commonly in obese, middle-aged women with type 2 diabetes. IR is considered to be central to the pathogenesis.[39]

Polycystic ovarian syndrome (PCOS) is a common metabolic disorder in women of reproductive age. In PCOS, IR and hyperinsulinemia are considered to cause ovarian steroidogenic dysregulation that leads to excess ovarian androgen production and anovulation. There is a clear association between PCOS obesity and type 2 diabetes and up to 40% of women with PCOS demonstrate some degree of glucose intolerance.[40,41] PCOS is also a risk factor for GDM, CVD, and endometrial cancer.[42] Acanthosis nigricans is a velvety thickening and darkening of the skin found especially on the back of the neck and axillae that is associated with IR. It is frequently seen in patients with PCOS.

Similarities Between GDM and the MS

GDM affects between 5% and 20% of pregnant women depending on the diagnostic criteria used and has many of the pathophysiological, clinical, and biochemical features of the MS.[15,43] These abnormalities occur with increased frequency relative to

non-GDM subjects antepartum, postpartum, and in the long term. As in the MS, IR is central to the pathogenesis of GDM. GDM patients are generally overweight and have a higher prepregnancy weight and BMI than non-GDM controls. They also have higher fasting and postprandial insulin levels, and lower HDL. GDM, like the MS, is predictive of type 2 diabetes. GDM may be considered to be a special presentation of the MS in pregnancy and the tip of the iceberg for a dangerous constellation of factors predisposing the patient to type 2 diabetes and CVD.[15]

Risk Factors for the Development of GDM

Risk factors for the development of GDM were evaluated in the Nurses' Health Study. This study followed over 100,000 nurses for an average of 10 years.[44] In another study of African–American women, risk factors for the development of GDM included obesity, older age, hypertension, family history of type 2 diabetes, and heart disease.[44] In a study of 1113 women who were at 21–28 weeks gestation, waist/hip ratio (WHR) and waist circumference were independently associated with two-hour glucose levels after a glucose tolerance test (GTT). These measurements were independent predictors of gestational glucose intolerance.[45] Change in waist circumference at this stage of pregnancy is mainly the result of central fat deposition.

IR in Pregnancy

Pregnancies complicated by GDM are characterized by an inability to increase insulin secretion to compensate for the increase in IR that occurs normally in pregnancy.[46,47] A pancreatic beta-cell secretory defect is present in both obese and lean women with GDM. Data demonstrate that overweight women who develop GDM have IR prior to pregnancy as measured by hyperinsulinemic-euglycemic clamp studies. Insulin-mediated glucose disposal decreases progressively in the second and third trimester of pregnancy and is about two-thirds that of normal pregnant women matched for weight. Furthermore, although women with GDM improve their IR postpartum, they never achieve the same degree of insulin-mediated glucose disposal as do normal pregnant women.[48]

GDM as a Predictor of Type 2 Diabetes

Women with GDM are at a significantly increased risk of developing type 2 diabetes. O'Sullivan[49] showed that the 15-year prevalence of type 2 diabetes in women with a history of GDM was approximately 60% for women who were obese and 30% for women who were lean. Mestman et al.[50] followed 360 women, mostly Latinas, with GDM for up to five years. Of 51 women with elevated fasting glucose during pregnancy, only four had a normal GTT six weeks postpartum. Of those 118 women with abnormal GTT but normal fasting glucose, 12.7 % developed overt type 2 diabetes and 32.6% abnormal GTT at the end of the study. Kjos et al.[51] followed 671 Latino women with GDM and a normal oral glucose tolerance test (OGTT) 4–16 weeks postpartum for up to 7.5 years. There was a 47% cumulative incidence rate of type 2 diabetes five years after delivery. In a meta-analysis, Kim et al.[52] concluded that differences in lengths of follow-up, ethnic variation, and the diagnostic criteria used accounted for most of the difference in risk between studies. The greatest risk factor for early-onset type 2 diabetes after pregnancy was early gestational age at the time of diagnosis and elevated fasting glucose.[53,54] The greatest long-term risk factor was maternal obesity.[55]

GDM and Subsequent CVD

Until recently there has been little data to demonstrate an increase in cardiovascular complications in women with GDM.[56] Carr et al.[57] reported that women who had a personal history of gestational diabetes in addition to a family history of type 2 diabetes had more CVD risk factors and more CVD events at a younger age than women with no prior history of GDM. Shah et al.[58] confirmed this increased risk and attributed it mostly to an increased prevalence of type 2 diabetes. Finally, recent work by Kessous et al.[59] demonstrated GDM to be an independent risk factor for cardiovascular morbidity over a decade later.

GDM and Dyslipidemia

During pregnancy, GDM induces a state of dyslipidemia characterized by elevated TG concentrations, as seen in other states of increased IR. However, GDM seems to blunt an increase in low-density lipoprotein (LDL) cholesterol.[60] As dyslipidemia is a component of the MS it is not surprising that this occurs commonly following GDM.[61] Kjos et al.[62] evaluated fasting lipids in a large cohort of Latino women with GDM during the first 36 months postpartum. Overall, the prevalence of high-risk LDL was no different from that of control subjects. However, increased TG and decreased HDL were found in subjects who developed diabetes during the study period. These findings were similar to those reported in the San Antonio Heart Study.[63] In another study of 56 former gestational diabetic mothers and 48 control mothers 5–6 years postpartum, mean TC, TG, LDL, and glucose were significantly higher in the GDM mothers than in the control mothers.[64]

GDM as a Predictor for Subsequent Development of the MS

Several studies have reported a greatly increased risk of MS following GDM.[65,66] Bo et al.[67] reported on the development of MS in a group of 81 women with prior GDM. Prevalence of the MS and its components was two- to fourfold higher in women with prior gestational hyperglycemia and 10-fold higher if pre pregnancy obesity coexisted when compared to normoglycemic controls, suggesting that GDM, especially in combination with prepregnancy obesity, predicts a subsequent syndrome of high cardiovascular risk. Verma et al.[68] confirmed this finding. They reported that 27% of 106 patients with GDM and 8.2% of 101 controls developed features of IR by 11 years after delivery. The cumulative hazard for developing MS in the next two years was 26 times higher among GDM subjects with prepregnant obesity, compared with controls. It was concluded that obesity and GDM in a prior pregnancy are significant risk factors for developing MS and cardiovascular risk factors. Pallardo et al.[69] in Spain studied 788 Caucasian women with GDM 3–6 months postpartum. Forty-three (3.7%) were diagnosed with overt DM. The area under the postpartum glucose curve was positively associated with BMI, waist circumference, WHR, TGs, and systolic and diastolic blood pressures. It was concluded that postpartum glucose intolerance predicts a high-risk cardiovascular profile that includes risk factors besides type 2 diabetes.

Gestational Hypertension, Glucose Intolerance, and Future MS

Pregnancy-induced hypertension (PIH) has now convincingly been related to glucose intolerance and IR.[70] Carr et al. reported that the rate of PIH was 17.0% in individuals with two abnormal values on a three-hour oral glucose tolerance (OGT), 10.8% with one abnormal value, and 4.6% with no abnormal value.[57] Pouta et al. reported on the six-year outcome in 45 women hospitalized with PIH. There was more hypertension, increased waist:hip circumference, increased serum insulin, and a lower glucose:insulin ratio in the PIH patients than the previously normotensive women. There was, however, no difference in lipids.[71]

Diagnosis of MS in Pregnancy

There is no generally recognized formal definition for the MS in pregnancy. In a recent study of 600 pregnant women by Bo the following criteria were used:

1. One abnormal value on the OGTT or GDM or hyperinsulinemia (≥2 SD above the mean for the 100 women with negative oral glucose challenge test used as controls)
2. Plus any two of the following:
   a. Blood pressure (BP) > 140/90
   b. TG > 2 SD above mean from control
   c. Low HDL-C < 1.0 mmol/L)
   d. BMI > 30
   e. Waist > 2 SD

The prevalence of the MS was 0% in women with a normal challenge test; 4.9% in those women with abnormal challenge and normal tolerance test; 20% in those with one abnormal value; and, 18% in gestational diabetes patients. Furthermore, worsening of GTT was directly associated with age, weight, BP, waist circumference, TG, and insulin levels and inversely associated with HDL-C values.[72]

Consequences of Maternal GDM and Type 2 Diabetes for the Offspring

It is well recognized that type 2 diabetes and GDM are associated with neonatal complications in the offspring, particularly relating to macrosomia and hyperinsulinism. However, it is now also recognized that in utero hyperinsulinism and over nutrition are associated with significant long-term problems for the offspring, notably obesity and type 2 diabetes.[73] Freinkel[74] hypothesized in his fuel-mediated teratogenesis theory that teratogenesis can occur after organogenesis during the differentiation and proliferation of fetal cells. Such changes could cause long-range effects upon behavioral, anthropometric, and metabolic functions. An increase in obesity in offspring of diabetic mothers that appears to be independent of genetic predisposition has been known for some time.[75] Offspring of diabetic women, even those who are of normal birth weight, have a higher mean weight relative to height at 5–19 years of age than do offspring of nondiabetic and prediabetic women.[76] Studies in Pima Indians found that type 2 diabetes occurs more often in offspring of diabetic mothers than in offspring of prediabetic or nondiabetic women (45% vs. 8.6% or 1.4%, respectively).[77] In a recent study of 126 overweight Hispanic children with a family history of type 2 diabetes, there was a high prevalence of features of the MS as noted previously. Insulin sensitivity was positively related to HDL and negatively related to TGs and systolic and diastolic blood pressures. Insulin sensitivity significantly decreased as the number of features of the MS increased.[22]

These observations have major implications for the management of obesity and type 2 diabetes. The data suggest that careful management of maternal metabolism in utero could help break the vicious cycle of obesity; GDM and type 2 diabetes and children of mothers with GDM or type 2 diabetes should be evaluated early to enable detection and management of the MS.[78]

PART 1 SUMMARY

The MS is a cluster of risk factors for CVD and type 2 diabetes associated with IR. GDM may be considered a special case of the MS occurring in pregnancy. It has similar risk factors, clinical and biochemical features, and long-term consequences. It is important to recognize individuals with MS and GDM so that early intervention can begin to modify these risk factors and delay or even prevent the progression to type 2 diabetes and CVD.

PART 2: MANAGEMENT OF THE MS

Delaying or preventing type 2 diabetes and early detection and treatment of cardiovascular risks factors are the main goals in the management of the MS. Although there is still need for high-quality studies to inform best management, a rational and aggressive approach is strongly recommended following delivery.[47,79,80]

Postpartum Evaluation of Women With GDM

Women with GDM should be seen 1–4 months (typically about six weeks) postpartum; an assessment of risk factors for future type 2 diabetes is done at this first visit along with a fasting plasma glucose (FPG) or an A1c and preferably a blood sugar level two hours after a glucose load (Figure 24-2).[79] The American Diabetes Association criteria for the diagnosis of type 2 diabetes and other forms of glucose intolerance are shown in Table 24-2.[81] A recent systematic review and meta-analysis by Bellamy et al.[82] reported a relative risk of 4.7 within five years of delivery and 9.3 five years after delivery. In one of the studies included in this review by Feig et al.,[83] the incidence of type 2 diabetes in women with previous GDM was 3.7% 9 months postpartum, 4.9% 15 months postpartum, 13.1% 5 years postpartum, and 18.9% 9 years postpartum but only 2% in the non-GDM controls). The strongest association is with waist circumference and BMI.[84] Other important risk factors are diagnosis of GDM prior to 24 weeks gestation; use of insulin during pregnancy; auto antibodies; higher glucose levels at diagnosis, during pregnancy, and on OGTT; and neonatal hypoglycemia. High birth weight and parity and a first degree relative with type 2 diabetes are of lesser risk.[85,86] Specific ethnic groups (Latinos, Asians, Native Americans, and African Americans) are at increased risk.[87] In addition, other risk factors such as cigarette smoking, family history of obesity, and cardiovascular risk factors should be carefully evaluated and updated on a regular basis.

All women regardless of the result of the GTT should be advised about their risk factors for future type 2 diabetes and

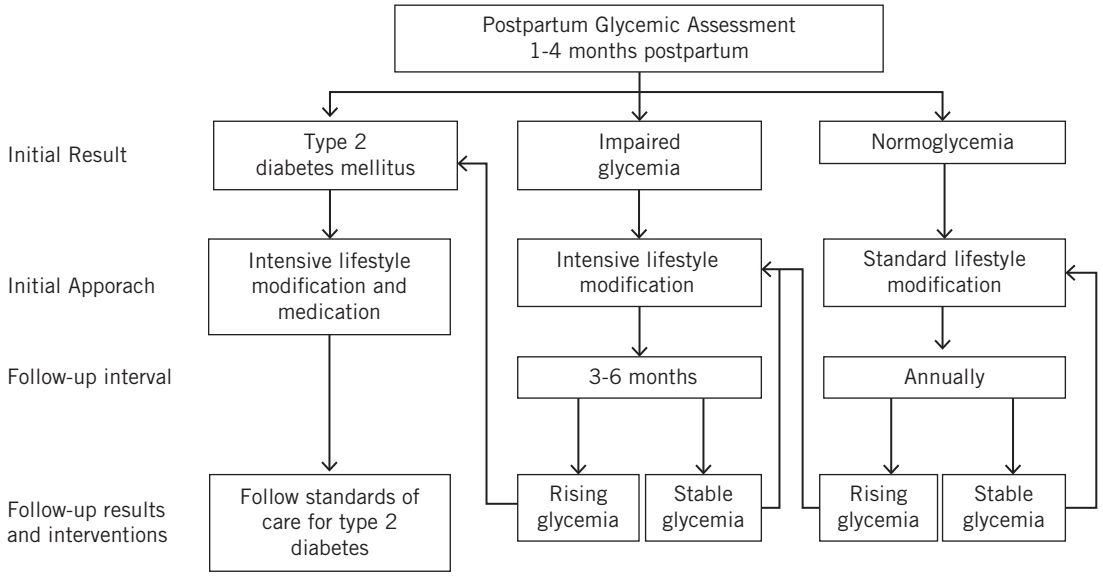

Figure 24-2 Management of GDM after pregnancy. (Adapted from Nature Reviews.[79])

TABLE 24-2 Diagnosis of Prediabetes and Diabetes Mellitus. Any One of the following

Measure	Prediabetes	Diabetes	Comment
A1c	5.7%–6.4%	>6.5%[a]	The test should be performed in a laboratory[b]
Fasting plasma glucose	100–125 mg/dL (5.6–6.9 mmol/L)	>126 mg/dL[a] (7.0 mmol/L)	Fasting for at least 8 h
2-h plasma glucose during an OGTT.	140–199 mg/dL (7.8–11.0 mmol/L)	>200 mg/dL[a] (11.1 mmol/L)	Glucose load of equivalent of 75 g anhydrous glucose dissolved in water
Random plasma glucose	—	>200 mg/dL (11.1 mmol/L)	In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis

[a]In the absence of unequivocal hyperglycemia, result should be confirmed by repeat testing.
[b]Using a method that is NGSP (National Glycohemoglobin Standardization Program) certified.
Source: Adapted from Diabetes Care 2013.[81]

CVDs. Ways of improving their risk factors through smoking cessation, proper meal plan, regular exercise, and achieving an ideal BMI should be discussed. This set of recommendations should extend to their immediate family. They should be seen at least on a yearly basis. Because the majority of women with GDM have been instructed on glucose self-monitoring, it is reasonable to advise them to measure their fasting glucose on a regular basis, perhaps monthly, and report to the physician if the glucose values are consistently over 100 mg/dL. Those with abnormal glucose metabolism need to be seen more frequently, home glucose self-monitoring encouraged and pharmacological intervention considered, if the goals are not achieved with a proper meal plan and increase in physical activity.[79] For completeness of the postpartum evaluation, BMI and BP are recorded and lipid levels measured 6–12 months postdelivery.

Prevention or Delaying Onset of Type 2 Diabetes

Several landmark studies in the last few years have demonstrated that progression to type 2 diabetes can be significantly delayed, and perhaps even prevented, by lifestyle modification and drug

therapy. Controlled trials have demonstrated that 7%–10% weight loss and exercise of approximately 150 min/ wk is highly effective in delaying the progression to type 2 diabetes in subjects with IGT.[13,88–90] In a study from China of 577 patients with IGT, a diet and physical activity program for six years was associated with a 30%–40% risk reduction for type 2 diabetes in both normal- and overweight subjects.[88] In the U.S. Diabetes Prevention Program, 3234 subjects with IGT were originally divided into four groups and followed for an average of 2.8 months.[13] The study comprised (a) a placebo or control group; (b) a metformin group (850 mg twice a day); (c) a lifestyle modification group with regular nutrition counseling and exercise under professional supervision; and (d) a Troglitazone group that was discontinued when the drug was withdrawn from the market. There was a reduction in progression of 58% in the life modification group as compared to 20% in the placebo group. Similar results were reported in the Finnish Diabetes Prevention Study (522 subjects) in which a life modification approach was used (sustained up to six years).[89,90]

Potential Drug Therapy

Given the poor long-term success of lifestyle modification, drugs from several different classes have been evaluated for their ability to delay progression from prediabetes to diabetes and have been shown to delay progression to type 2 diabetes. In the Diabetes Prevention Program, the subgroup receiving metformin had a 31% relative reduction in progression to type 2 diabetes at 2.8 years.[13] In the Troglitazone in the Prevention of Diabetes (TRIPOD) Study, 235 Hispanic women with previous gestational diabetes were randomized to receive placebo or troglitazone. At the end of two years, a 58% relative risk reduction for type 2 diabetes was reported in the women on troglitazone that persisted after a washout period of more than eight months.[91] However, currently there is no evidence that the benefit of initiating drug treatment for prediabetes outweighs the risks or is superior to initiation of drug treatment once diabetes has developed. The 2013 American Diabetes Association Clinical Practice Recommendations are that metformin therapy may be considered to prevent diabetes in individuals with IGT, impaired fasting glucose (IFG), and an A1c of 5.7%–6.4%, especially in those with a BMI >35 kg/m,2 <60 years of age, and prior GDM.[81]

In summary, a consistent lifestyle modification approach is very effective in controlling the progression to type 2 diabetes in high-risk populations: the problem is the well-known inability for patients to adhere to these programs in the long term. Pharmacological therapy in prediabetes appears encouraging, but not enough information is available to recommend it at present.

Treatment of Type 2 Diabetes

For the vast majority of those affected, type 2 diabetes is a chronic disease and lifelong care is required. There are several components to care. A summary of these can be found each year in the American Diabetes Association Clinical Practice Recommendations.[81] Key points from these recommendations are discussed here.

Diabetes Self-Management Education and Support

Education of patients regarding their diabetes is fundamental to care. Certified Diabetes Educators are available in most communities and they play an important role in management. Every person with type 2 diabetes should receive diabetes education: they should learn about self-care, self-monitoring of glucose at home, critical glucose values, what to do during sickness, and so forth. Teaching should be ongoing with regular visits to care providers.

Lifestyle Management

Several studies have shown benefit of a modest loss of 7%–10% of body weight through lifestyle intervention in individuals with prediabetes.[13,88–90] However, the recent Look AHEAD study showed no significant benefit in its primary outcome, a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina during a maximum follow-up of 13.5 years although other benefits, including less use of medication and greater mobility were noted.[92] Currently, expert opinion still endorses lifestyle modification for the majority of individuals with type 2 diabetes.[81]

Meal Plan

Although in daily practice this is a very difficult task, patients should be encouraged to at least not gain weight. The latest recommendations from the American Diabetes Association are based mostly on expert opinion and data from single high-quality clinical trials and poorly controlled or uncontrolled studies.[81] This includes the following recommendations: the proportions of macronutrient (carbohydrate, protein, and fat) may be adjusted to meet individual metabolic goals and preferences, monitoring of carbohydrate intake is central to achieving glycemic control, saturated fat intake should be 7% of total calories, intake of trans fat should be minimized to lower LDL, alcohol should be limited to one drink per day or less for adult women and two drinks per day or less for adult men, and extra precautions should be taken to avoid hypoglycemia in those who use alcohol. High-quality studies have not demonstrated benefit from routine supplementation with antioxidants such as vitamins E and C and carotene, and as their long-term safety is unknown these are not recommended. Finally, it is recommended that meals are planned so that an individual's need for all micronutrients are met.[81]

Physical Activity

The American Diabetes Association considers there is strong evidence to recommend that adults with diabetes perform at least 150 min/wk of moderate-intensity aerobic physical activity (50%–70% of maximum heart rate), spread over at least 3 d/wk with no more than two consecutive days without exercise and, in the absence of contraindications, they should be encouraged to perform resistance training at least twice per week.[81] It is now recommended that health care providers use clinical judgment to determine the extent of evaluation for CVD before initiation of an exercise program in asymptomatic patients as screening for coronary artery disease in such individuals remains of unproven benefit.[81]

Depression

Depression is common and should be screened for and treated with behavioral therapy and/or medication.as it frequently impairs quality of self-care and medical outcomes.[81]

Drug Therapy

Drug therapy for diabetes is evolving in several ways. First, instead of recommending a standard approach for all patients there is a move toward a personalized approach that takes into account an individual's "ABCDE" which refers to their age, body weight, complications (microvascular and macrovascular), duration of diabetes, and life expectancy as well as the expense of therapy.[93] Second, there is a move to treat individuals more aggressively with multiple different agents with different modes of action soon after diagnosis rather than with the current standard of starting with a low dose of monotherapy and increasing the dose and number of medications when the patient fails to maintain glycemic control on that regimen.[93–95] Glycemic target should also be individualized, with a goal A1c of <7% for most patients but <6.5% may be appropriate if this can be achieved safely. Regular reassessment of diabetic control is essential to keep A1c within target values. Potential side effects of each drug must be discussed with the patient at the onset of therapy.[81]

Over a variable period, ranging from months to years, the efficacy of noninsulin agents in controlling glycemia diminishes as endogenous insulin production by the pancreas declines. At this time, insulin therapy becomes necessary to maintain normoglycemia. Several different insulin formulations are available that differ in time of onset and duration of action. Different administration regimens are used. A patient with type 2 diabetes may use a single nighttime dose of neutral protamine hagedorn insulin (NPH) or Glargine to suppress basal glucose levels and continue with oral agents during the day. Eventually, multiple daily injections may be needed.

Bariatric Surgery

Bariatric surgery is now recognized to be highly effective therapy for type 2 diabetes in many individuals. High cost and safety concerns limit wider use. The American Diabetes Association now recommends that adults with BMI >35 kg/m^2 and type 2 diabetes be considered for bariatric surgery especially if the diabetes or associated comorbidities are difficult to control with lifestyle and pharmacological therapy.[81]

The majority of patients with type 2 diabetes present with identifiable cardiovascular risk factors at the time of diagnosis. In addition to management of hyperglycemia, dyslipidemia, hypertension, and obesity should be aggressively managed to prevent micro- and macrovascular complications.

Treatment of Dyslipidemia

Low HDL levels and high TG are typical of the MS. Small, dense LDL particles, known to be atherogenic are increased, although the total LDL levels may be within normal limits or only slightly elevated. The initial approach to the management of dyslipidemia is lifestyle modification. Drug therapy is indicated if, after a period of about three months, target values are not achieved.[81] Statin therapy is very effective in achieving TC and LDL target values. Statins are in general well tolerated. Liver function tests are recommended at six weeks after initiation of therapy. Muscle aches and cramps are reported in a small group of patients and occasionally the drug has to be discontinued. Fibrates are the most effective agents for lowering TGs (25%–50%); they also raise HDL by 10%–20%. Niacin is also very effective at raising HDL (15%–35%) and lowering TGs (20%–40%). However, it has a tendency to increase IR and worsen glucose levels.[81]

Treatment of Hypertension

Hypertension should also be treated initially with lifestyle modification. Every person with type 2 diabetes with persistent BP readings of 130/80 or higher should receive pharmacological therapy. ACE-I and ARB's are generally initial drugs of choice. An annual determination of microalbuminuria, a risk factor for the development of nephropathy and CVD, is recommended. Patients with persistent microalbuminuria should be treated with ACE-I or ARB drugs.[81]

Aspirin

Aspirin is highly effective in secondary prevention of myocardial infarction and stroke, but its use for primary prevention of CVD is controversial. Consequently, the American Diabetes Association recommends routine use in those with a history of CVD and that it be considered for use in those at high risk for this.[81]

Cigarette Smoking

Cigarette smoking is the major preventable cause of disease in the United States, causing more than 440,000 deaths annually. It may play a role in the development of diabetes and is a major risk factor for CVD. All patients should be advised not to smoke and counseling, behavior modification techniques, and pharmacotherapy with nicotine or bupropion should be considered as therapy.[81] Long-term follow-up should be available to prevent relapse.[81]

PART 2 SUMMARY

GDM is frequently the first indication of type 2 diabetes and the MS. Because these conditions are asymptomatic at onset, it is imperative for the health care professional to actively investigate for early metabolic abnormalities, to offer counseling with the assistance of other health care professionals, such as nutritionists and diabetic educators, and to extend these recommendations to the entire family. Preconception counseling is an integral part of this approach. It is expected that an active integrated program will prevent the alarming increase in the incidence of obesity, type 2 diabetes, and the MS in our society.

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Screening for Gestational Diabetes

25

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To screen or not to screen, we have lots of questions:
Why? Who? How? and When?

—Anonymous

Key Points

- Justification for screening is determined by severity of the disease and existence of an intervention that will decrease adverse outcome
- Screening will unmask a cohort of women who have or will develop type 2 diabetes
- Selective or universal screening should also be determined by population characteristics
- The 50-g one-hour oral glucose challenge test (GCT) performed without regard to meal, dietary preparation, or time of day
- Glucose threshold for abnormality between 130 and 140 mg/dL should be selected based on the rate of patients at risk in the population
- The purpose of a screening test is to identify the patient at risk to have a disease, but screening results should not be equated with adverse outcome from the disease

INTRODUCTION

To screen or not to screen is ultimately a function of the magnitude of the adverse outcome of a potential disease in pregnancy. Different diseases have varied rates and severity of complications. Therefore, the primary mission in screening for diabetes in general and gestational diabetes in particular justify the effort and cost of early identification in patients at risk for the disease. Even with identification, justification for screening will be determined if an intervention exists that decreases the adverse outcome with timely initiation.

Diabetes is the fourth leading cause of death in the United States. It is the leading cause of blindness in adults, kidney disease/failure, and most nontraumatic, lower extremity amputations. Those with diabetes are twice as susceptible to heart disease and two to six times more likely to have a stroke. Diabetes increases coronary heart disease twofold in men and fourfold in women; it is responsible for 50%–60% of adult deaths in the United States. In addition, cardiovascular disease, which is the cause of death in 75% of the diabetic population, begins to develop during the "pre-diabetic phase."[1,2] It is also a common cause of perinatal complications including mortality, fetal macrosomia, metabolic and hematological complications, shoulder dystocia, and long-term effects on the child.

The majority of studies have used fetal outcome as the endpoint of whom to screen. However, maternal outcome such as the future onset of diabetes, in and of itself, may be a valid argument for initiating screening in pregnancy. Approximately 9% of gestational diabetes mellitus (GDM) women are undiagnosed type 2 diabetics. Type 2 diabetes represents the archetype of a chronic degenerative disease. It has become epidemic with more than 170 million cases to date worldwide.[3–5] Moreover, more than 20%–40% of women in the United States are now obese or overweight prior to conception. In addition, GDM is more common among certain ethnic groups such as African–American, Asian, Hispanic, and Native American women, compared with non-Hispanic white women. Since these high-risk groups are unevenly distributed in the United States, different geographic groups will have a disproportionate prevalence of GDM, that is, San Antonio, Texas, and New Orleans, Louisiana.[6,7]

Approximately 20% of patients with "newly" diagnosed type 2 diabetes have eye, nerve, or kidney disease at the time of diagnosis.[8] Furthermore, many GDM women are at increased risk for subsequent development of type 2 diabetes (6.8%–92% when impaired glucose tolerance test is combined with overt diabetes, and 3%–50% for overt diabetes alone).[9–11] Overall, 50%–75% of GDM patients will have the likelihood to develop type 2 diabetes. It is projected that approximately 50% of women with GDM will develop diabetes 22–28 years after pregnancy.[6,7] Approximately 60% of Latin American women with GDM may develop type 2 diabetes within five years after the index pregnancy.[12] Thus, type 2 diabetes and gestational diabetes may arguably be the same

disease with different names that are identified based on disease severity and diagnosis criteria. Finally, lean GDM women with positive islet-cell antibodies may develop type 1 diabetes (about 5% of the GDM population).[12–15]

Screening is not a diagnostic method and screening results are not pathognomonic for the disease. Screening identifies, in an asymptomatic population, those who are at risk to develop the disease and who may require more specific testing to determine if treatment is needed. The tests are administered to healthy patients and often to entire relevant populations. The ideal screening test needs to be inexpensive, easy to administer, and interpret and not associated with significant discomfort or inconvenience.

Three conditions need to be met for early detection: (1) the results must provide clinically important gains, (2) the benefits must exceed the negative effects of testing, and (3) the net benefit (total benefit less the total harm) must justify the economic costs of testing and treatment. Thus, the main purpose of screening and intervention is net improvement in health outcomes at affordable economic costs (Table 25-1). As described earlier, screening is the testing of apparently well people to find those at increased risk of having a disease. It should be noted that the results of screening should not be equated with a diagnosis of a disease and its follow up treatment.

Four distinct terms define the validity of a screening test: *sensitivity*, *specificity,* and *predictive value of positive and negative results.* Blood glucose is a continuous variable; therefore, sensitivity and specificity are inversely related. The cutoff for abnormal is selected based on the concept of correlated normality; it identifies the threshold for a given outcome variable reflecting desired/undesired outcome. The prevalence of a disease in a population affects screening test results, that is, in low-prevalence settings, even very good tests have poor predictive value positives. Therefore, it is mandatory that there be knowledge of the approximate prevalence of the disease in a given population to more accurately interpret screening test results.

There needs to be an available screening test with sufficient sensitivity and specificity to achieve the goal of decreased morbidity and mortality. It is important to determine the probability of a positive test result if the disease is truly present (sensitivity). A high sensitivity reduces the number of women with gestational diabetes, who are missed by the screening test. It is also important to determine the probability of a negative test result when it is truly absent (specificity). As specificity increases, the number of women without gestational diabetes, who are incorrectly classified as positive decreases. A sensitive screening test will rarely be negative when the disease is truly present (false-negative results) and a specific screening test will rarely be positive when the disease is truly absent (false-positive results). In addition, the probability of the disease being present when the test result is positive (positive-predictive value) and the probability of the disease being absent when the test result is negative (negative-predictive value) must be considered. As a general rule, the validity of a test is enhanced as the sum of the sensitivity and specificity of a test are increased.

The predictive values are a function of the sensitivity and specificity of the test as well as the prevalence of the disease in the population. The sensitivity and specificity of a screening test may be altered by the definition of an "abnormal" test result. The determination of a cutoff for normal is a compromise between increasing sensitivity and decreasing specificity. For example, lowering the threshold for an abnormal test will result in a more sensitive test with fewer false-negative results. The same manipulation, however, also increases the probability of false-positive results and, therefore, decreases specificity. A relatively simple and practical approach to determining the most efficacious screening method is to add the specificity and sensitivity values. The higher the sum equates with the superior method (Table 25-2).

There are four possible options when considering screening for GDM. *Mass (universal) screening* provides early detection for an entire population. *Selective screening* is applied to a subset of high-risk individuals drawn from a larger population. *Case finding* refers to an "opportunistic finding" in which a test is used on persons who entered the health care system for other reasons. The fourth option is *not to screen*. Using this last option, the physician a priori makes the determination to treat the complications as they develop instead of applying early detection with the potential to prevent complications.

O'Sullivan found the presence of risk factors in 37% of his study population with a sensitivity of 63%.[16] When the threshold was decreased to a screening of 130 mg/dL, the sensitivity increased to 79%. Limiting screening to risk factors for GDM, such as family history, obesity, previous macrosomia, congenital anomalies, glycosuria, and so forth, alone will miss 50% of cases.[17–19] In contrast, in patients without the above risk factors (low-risk group), the prevalence of GDM is approximately <1%. Therefore, not screening the low-risk group will result in missing 10% of GDM cases of which approximately 16% would probably have required pharmacological therapy.[20,21] The Fourth International Workshop-Conference on Gestational Diabetes Mellitus recommended that in low-risk women blood glucose testing is routinely required (Table 25-1). In average-risk patients, blood glucose testing needs to be performed at 24–28 weeks' gestation using the two-step approach (50-g challenge test followed if needed by oral glucose tolerance test [OGTT]) or one-step procedure to all subjects (diagnostic OGTT). For high-risk patients, blood glucose testing should be performed as soon as feasible.[22] Universal screening for GDM maximizes screening sensitivity, but it is less cost-effective than selective screening. In addition, the 50-g one-hour glucose screening test at 24–28 weeks' gestation offers the best combination of ease and economy of use and reproducibility in screening for GDM. The 50-g one-hour screen threshold for abnormality must be low enough to optimize sensitivity but not so low that an inordinate proportion of the screened population is referred for confirmatory testing.[23] The American Diabetes Association[24,25] proposed that all pregnant women undergo risk assessment for GDM at the first office visit

TABLE 25-1 Low-Risk Status for GDM

Low-Risk Status
• Age <25 years
• Weight normal before pregnancy
• An ethic group with a low prevalence
• No known diabetes in first-degree relatives
• No history of abnormal glucose tolerance
• No history of poor obstetric outcome

TABLE 25-2 Screening Test for Gestational Diabetes

	Specificity	Sensitivity	Total
50-g 1-h, 140 mg/dL	87.0	79.0	166
50-g 1-h, 135 mg/dL	80.0	98.0	178
50-g 1-h, 130 mg/dL	78.0	100.0	178
Fructosamine	79.0	77.0	156
Random glucose >6.4 Mm, 2 h after meal	96.0	16.0	112
Urine glucose 1st Trimester	99.0	7.0	106
Fasting glucose of 4.7 mM	68.0	68.0	136
Fasting glucose of 4.9 mM	40.0	80.0	120
Fructosamine	77.0	79.0	156
Glycohemoglobin	87.0	27.0	114

as early as possible. In contrast, pregnant women who fulfill all of the factors in the low-risk criteria need not be screened for GDM. Women with risk factors for GDM are those with a previous medical history of GDM, known impaired glucose metabolism, and obesity (BMI ≥ 30). In this high-risk group, if GDM was not diagnosed during early screening, blood glucose testing should be repeated at 24–28 weeks gestation.[26,27]

American College of Obstetricians and Gynecologist (ACOG)[28] recommends that all pregnant women be screened for GDM whether by the patient's medical history, clinical risk factors, or laboratory screening test. It is recommended that blood glucose screening be performed between 24 and 28 weeks of gestation. Early screening should be performed on patients that are potentially undiagnosed type 2 diabetics or within the high-risk criteria for GDM. In these patients, if the early screening results are negative, testing should be repeated at 24–28 weeks' gestation. In practice, many physicians elect to screen all pregnant women as a practical consideration. Although the above recommendations are useful and cost-effective for some demographic/geographic regions, they may inadvertently cause confusion in others. For example, for a city such as San Antonio in which approximately 70% of the population is Mexican–American and the maternal age is relatively higher with a high rate of obesity, the majority of gravids will classify as high risk. Using the approach of selective screening will not decrease cost significantly and will enhance the rate of undiagnosed GDM. It is more efficacious for the practitioner to determine the approach of selective or universal screening based on the demographic/geographic profile of his patient mix.

ACOG has stated: "Although many care providers choose to screen high risk patients early in pregnancy, the benefit of treatment of women with GDM identified early in pregnancy has not been demonstrated but rather has been accepted on a theoretical basis."[28] Even though there is near standardization of current practice in the United States, there are several unresolved issues: the rationale behind routine screening, which screening method(s), and the glycemic values on screening tests that define "abnormal." The 2008 U.S. Preventive Services Task Force determined that "the current evidence is insufficient to assess the balance between the benefits and harms of screening women for GDM either before or after 24 weeks' gestation." The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) has proposed a one-step (fasting, one-hour and two-hour glucose measurements), where GDM is diagnosed by only one abnormal value.[29]

Although GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy, it is well recognized that a large segment of these women have impaired glucose tolerance test results or type 2 diabetes. In fact, millions of women in the United States suffer from type 2 diabetes and remain undiagnosed and, therefore, untreated. The motivating factor in early screening should be driven by the potential to identify type 2 or impaired glucose tolerance test in women. Early identification will explain undesired outcome such as spontaneous abortion and congenital malformations. Timely and appropriate treatment may mitigate some of the complications for both mother and fetus (e.g., preeclampsia). Therefore, early screening should be judged by its overarching universal benefit rather than the narrow view of pregnancy outcome in GDM.

Several risk factors are associated with increased risk for GDM. When maternal age is a major risk factor, every year after the age of 25, the relative risk to develop GDM increases by 4 (95% confidence interval 2%–6%). The incidence of GDM at <20 years of age is <1%; 20–30 years, 2%; >30 years, 8%–14%.[30] When maternal age >25 is used as a threshold for indication for screening, the cost may be decreased by as much as 50% with only 5% reduction in sensitivity from 79% to 74%.[31] For 25% of GDM women, a positive family history is found (relative risk, 1.68). When body mass index (BMI) is ≥30 vs. BMI <20, the incidence of GDM increases threefold. In addition, an increased waist to hip ratio is associated with increased risk for GDM. Ethnicity also plays a crucial role in the enhanced risk for the development of GDM (Asians: fivefold; Hispanic: 2.5-fold; African–American: twofold, in comparison to Caucasian women).[32,33]

There is paucity of evidence-based research comparing the different methods of GDM screening and what exists is often contradictory. Griffin et al.[34] in a randomized prospective study, assigned women to one of two groups: (1) universal screening at 26–28 weeks gestation and (2) women with risk factors for GDM at 32 weeks gestation. The results showed an increased prevalence of GDM diagnosed in the universal screening group

(2.7% vs. 1.45%; $P < 0.03$) and reaffirmed the poor predictive value of historical risk factors for diagnosing GDM (positive predictive value: 8.0%). The universally screened early diagnosis group had a higher rate of spontaneous vaginal delivery at term and lower rates of macrosomia, cesarean section, prematurity, preeclampsia, and admission to neonatal intensive care units. Drawbacks to this study include the following: (1) maternal age was not considered a risk factor for GDM thereby leading to an underestimation of the number of women who needed further testing; (2) performing diagnostic testing at 32 weeks gestation delayed diagnosis and initiation of treatment that could have possibly affected the rate of maternal–fetal complications; and (3) the small sample size (62 women with GDM).

In contrast, Wen et al.[35] showed in their population-based study that although the age adjusted incidence of GDM decreased after discontinuation of universal screening in the Metro-Hamilton (Canada) area in 1989, there was no corresponding change in the incidence of fetal macrosomia, cesarean delivery, preeclampsia, or polyhydramnios when compared with those in Ontario. It should be noted that perinatal outcome and decreased rate of complications is directly associated with treatment modality and level of glycemic control achieved in a study. Rather than concluding that the study had modest impact on outcome, it would have been preferable to question if participants had been treated in a timely and effective manner to influence perinatal outcome.

To reiterate, screening is a test performed on asymptomatic patients to identify those at risk for developing a disease. When success of treatment is evaluated, many confounders can affect outcome. Therefore, using outcome success rate as the rationale for or against screening is inappropriate since the confounder factors influencing outcome can mask the benefits of screening. Unless there is a concerted effort to optimize care after diagnosis, screening cannot be useful or cost-effective.

At present, there is a dichotomy between the European and United Kingdom approach of no screening and the American approach of universal screening. Some care providers in the United States perform universal screening; some authoritative bodies recommend selective screening. However, 97% of U.S. obstetricians screen for GDM[36–38] in contrast to 17% in the United Kingdom[39] and 84% in Canada.[40] The implications of the diagnosis of GDM goes beyond pregnancy in terms of health impact and labeling (e.g., for insurance purposes) for both mother and baby. The medical ramifications of this discrepancy cannot be ignored as this diagnosis or the lack of it will affect thousands of women and infants worldwide. Although we recognize the importance of evidence-based medical practice, clinical practices in this modern era are still derived from uncontrolled studies or expert opinion, with GDM practices being no exception.

Overdiagnosis may inadvertently label patients with a disease they do not have. In addition, modern technology and overutilization of screening tests can often detect ever smaller "abnormalities"; vested interests may have a stake in the process; overzealous panels who expand disease definitions and practice guidelines; legal incentives that punish under-diagnosis but not overdiagnosis; health care systems that overemphasize the concept of "prevention"; and traditional beliefs that espouse "more is better."[41,42]

The Second and Third International Workshop Conferences[43,44] on GDM recommended screening with a 50-g oral glucose load followed one hour later with a blood glucose determination as originally proposed by O'Sullivan et al.[16] These investigators recommended that patients with a value of 130 mg/dL or greater for the GCT should be followed up with an OGTT. In their data, this approach had a sensitivity of 79% and specificity of 87% for the diagnosis of GDM by the OGTT. To account for plasma determination, the cutoff was modified to 135 or 140 mg/dL and this threshold have been widely applied as the indication for a follow-up OGTT.

Investigators and clinicians are still divided on the threshold value that needs to be used for GDM screening. Coustan et al.[45] studied 6,000 women using a 50-g oral GCT with an abnormal threshold designated as 130 mg/dL. Twenty-three percent of his study population required a three-hour OGTT. Lowering the threshold from 140 mg/dL to 130 mg/dL resulted in an 11% increase in test sensitivity. However, there was a significant increase in the rate of women requiring OGTT. Studies have demonstrated that about 10% of individuals with screening results between 130 and 139 mg/dL will manifest GDM if tested with a three-hour OGTT (Table 25-3).To maximize the sensitivity and minimize the false-positive rate of the glucose-loading test, it may be efficacious to vary the threshold in consideration of ethnicity. However, without adequate evidence-based research findings, we will not know if improved perinatal outcomes can be achieved with modification of glucose-loading test thresholds.[46]

TABLE 25-3 Screening Threshold

	GDM (%)	Screen (mg/dL)
Sacks et al.[62]	10.0	135–139
Coustan et al.[63]	10.0	130–139
Dooley et al.[64]	11.5	130–139
Yalcin et al.[65]	2.7	130–134
	10.1	135–139
Yogev et al.[56]		
≥2 values	7.4	130–139
≥1 values	10.9	130–139

Others have studied the potential for BMI as a marker for GDM. They concluded that BMI can be used to counsel regarding the risk of developing GDM but BMI alone is not a good screening tool; in addition, they confirmed that GDM prevalence varies by race/ethnicity.[47] A secondary analysis of the data from a multicenter treatment trial of mild GDM to estimate the relationship between one-hour 50-g glucose challenge and perinatal outcome showed that GCT values of 135–140 mg/dL were not associated with adverse outcomes compared with values <120 mg/dL; however, GCT values of 140 mg/dL or higher were associated with adverse perinatal outcome, large-for-gestational age (LGA), and macrosomia.[48]

The most recent position statement of the ADA and ACOG[25,27,28] indicate that use of a threshold of 140 mg/dL results in sensitivity of 80%–90% and 15% of the patients will require a three-hour OGTT. The use of a cutoff of 130 mg/dL will increase the sensitivity to nearly 100% but will require OGTT in 23%–25% of the patients. Because the precise cost-benefit ratio for diagnosing GDM remains unresolved, either threshold is acceptable. The selection of the threshold should be decided mainly by demographic/geographic/ethnic considerations. In regions with a high prevalence of GDM/type 2 diabetes, it is reasonable to use the lower threshold (130 mg/dL—increasing sensitivity); in an area of lower prevalence, the cost-effectiveness will dictate the choice of a higher threshold, 135–140 mg/dL.

The upper threshold of screening for which an OGTT (diagnostic) is not indicated is debatable. Carpenter and Coustan[49] reported that the positive-predictive value of screening test thresholds between 175 and 184 mg/dL is 50%. They had six subjects with screening values >184 mg/dL, who had GDM. Gabbe and Graves[50] in a review article suggested that a diagnosis of GDM is inevitable with a screening value of 200 mg/dL. Therefore, an OGTT need not be performed and treatment should commence.

Our group demonstrated that with a threshold of 180–189 mg/dL, approximately 26%–34% of women were diagnosed with GDM by both the Carpenter–Coustan[49] and the National Diabetes Data Group criteria.[51] Above this threshold (≥190 mg/dL), 55% will have abnormal glucose tolerance test results. The differences in the findings can be partly explained by sample size, delay in stomach emptying, and timing of screening.[52–55] Thus, to prevent unnecessary treatment of normal individuals, a diagnostic test is recommended at this threshold level. Only in extreme levels, that is, ≥210–230 mg/dL, a diagnostic test is not required. As the screening values increase, there is an increased prevalence of GDM. In contrast, the rate of obesity is relatively stable (25%–30%) in screening levels between 130 and 189 mg/dL and only in thresholds of ≥190 mg/dL does the incidence of obesity increase to 57% (Table 25-4).[56]

The association between screening results in nondiabetic women and neonatal size, specifically LGA infants, remains divisive. We found two different patterns that represent the prevalence of LGA in obese and nonobese nondiabetic women. There is an approximate 12% prevalence of LGA in obese patients below screening results of 120 mg/dL. Thereafter, there is a twofold increase (from 12% to 25%) from a screening level of ≥120 mg/dL. For nonobese women, a similar rate of LGA was found with screening results of <130 mg/dL with a steady increase thereafter approaching 22%. Our data and those of others suggest that there is an independent association between pregravid BMI, gestational diabetes, and LGA in both gestational and nongestational diabetic women (Figure 25-1 and Table 25-5).[56–59]

TABLE 25-4 Prevalence of GDM and Screening Result

	GDM (%)	Screen (mg/dL)
Atilano et al.[66]	57	≥185
	87	≥190
Lanni et al.[67]	36	≥180
	47	≥200
	55	≥220
	57	≥240
Yogev et al.[56]	34	180–189
	52	190–199
	58	>200

Perucchini et al.[60] suggested the use of a fasting glucose value to screen for gestational diabetes. They compared the 50-g challenge test with fasting plasma from the OGTT using the Carpenter–Coustan criteria on each subject regardless of the screening results. They proposed that a 7.0 mmol/L screening value is the best threshold for the challenge test resulting in a sensitivity of 81% and specificity of 76%. The study further suggests that if a screening threshold of 4.8 mmol/L fasting plasma is used, 70% of the women will not need a diagnostic OGTT. However, this method missed 19% of GDM cases. When the threshold was reduced to 4.4 mmol/L, the result was a sensitivity of 100% and specificity of 39%. In another study, Reichelt et al. evaluated the sensitivity and specificity of fasting plasma glucose (FPG) in comparison to the 75-g OGTT. They found that a threshold of FGP of 4.9 mmol/L resulted in a sensitivity of

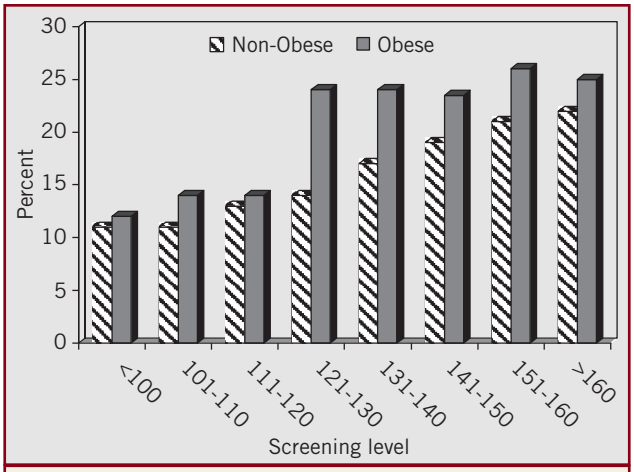

Figure 25-1 Stratification for LGA by GCT Severity. (Modified from Yogev et al.[56])

TABLE 25-5 Selected Pregnancy Outcome Measures in Obese and Nonobese Women Stratified by Glucose Challenge Test (GCT)

	GCT < 130 (n = 4313)		GCT ≥ 130 (n = 2077)	
	Obese n = 927	Nonobese n = 3386	Obese n = 602	Nonobese n = 1475
Birth Weight (g)	3313 ± 708	3258 ± 591	3462 ± 550	3337 ± 561
Macrosomia	12.9%	7.9%	17.8%	11%
Large for Gestational Age	21.3%	12.3%	24.6%	19.8%
Induction	16.7%	11.4%	12.3%	7.5%
Preterm Labor	9.8%	9.5%	10.8%	7.6%
NICU Admission	12.3%	11.5%	10.6%	9.4%
Respiratory Complications	8.7%	6.2%	7%	5.7%

*Modified from Yogev et al.[56]

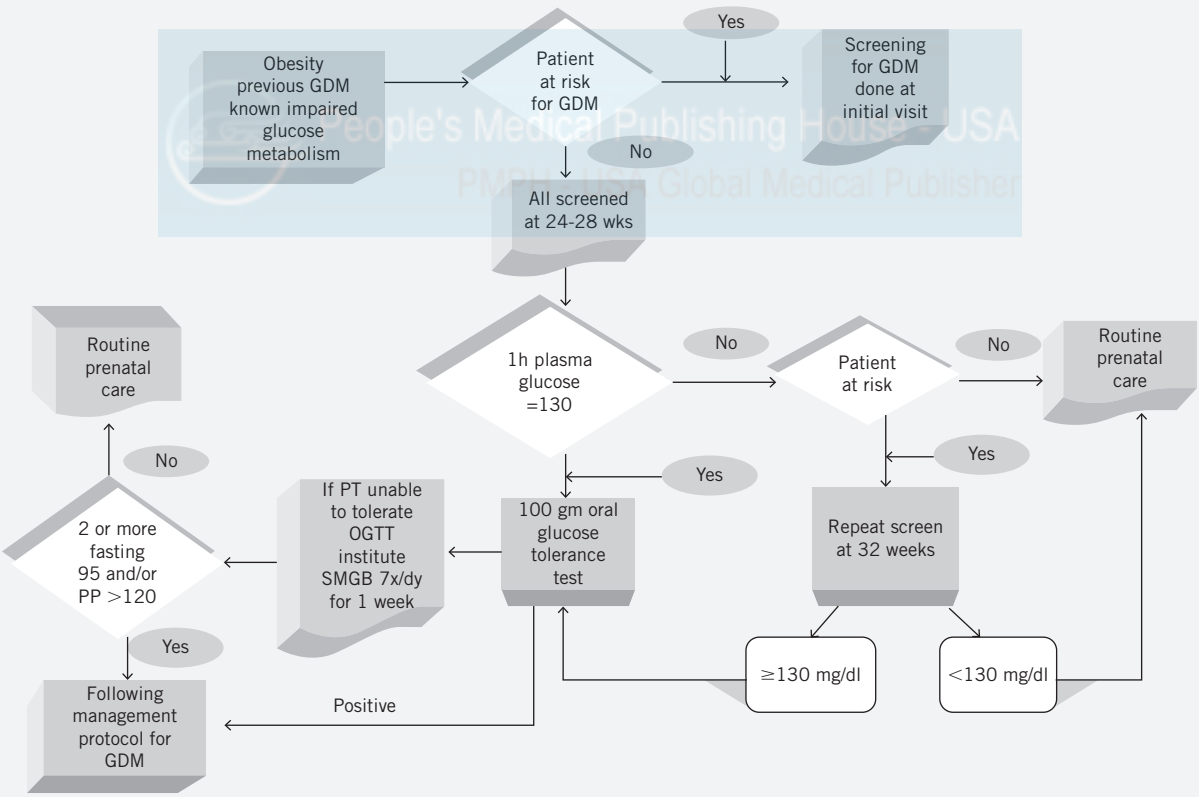

Figure 25-2 Decision tree for screening approach.

88% and specificity of 78% for diagnosing GDM. Twenty-two percent of the subjects in this study had values >4.9 mmol/L.[61] Sacks et al.[62] found that for FPG of 88 mg/dL, sensitivity equaled 80% and specificity equaled 40%; for FPG 84 mg/dL, sensitivity was 90% and specificity was 21%; for FPG of 81 mg/dL, sensitivity was 95% and specificity was 11%. Although using fasting plasma for GDM screening is an attractive approach, the relatively high rate of missed GDM diagnoses precludes current recommendation of this method.

SUMMARY

The clinical dilemma of screening for GDM is that authoritative bodies have failed to endorse either universal or selective screening. They have failed to establish a threshold criteria and method of screening that will be globally applicable. A recent survey[44] reported that routine screening for GDM is a common practice and is used by 96% of obstetricians in the United States; 95.2% used a 50-g GCT. Furthermore, in 1987, only 83.8% of ACOG members used universal screening and this increased to 96% in 2003. The survey did not report the different thresholds used for positive screening.[44]

The lack of consensus with firm recommendations for selective or universal screening by several authoritative bodies has not precluded obstetricians from almost uniformly using their own clinical judgment and universally screening their patients. The clinical wisdom dictates that type of screening, universal or selective, and threshold selection should be performed in conjunction with the population-specific profile. This practical, cost-effective approach will address patient needs and remove from the stage an artificial controversy that leads to sophistry and pontification at public expense (Figure 25-2).

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Gestational Diabetes: A Diagnostic Dilemma?

26

A Difference, to be a Difference, Must Make a Difference

Oded Langer, MD, PhD

The little present must not be allowed to elbow the great past out of view

—Andrew Lang

Key Points

- The most commonly accepted method of diagnosis of gestational diabetes mellitus (GDM) in the United States is the 100-g oral glucose tolerance test (OGTT) using the National Diabetes Data Group (NDDG) criteria
- The pathophysiology of women with one abnormal value is comparable to those with two or more abnormal values on the OGTT
- Similar adverse perinatal outcome is found in women with one abnormal and untreated GDM
- Two currently recommended diagnostic approaches are the one- and two-step methods
- Postpartum (6–8 weeks) 75-g OGTT should be administered to all GDM women. The test should be repeated on a regular basis every 1–3 years depending on the risk factors for developing type 2 diabetes

INTRODUCTION

The subtitle of this chapter, ascribed to the author Gertrude Stein, should focus our critical sensibilities on the evaluation of a change in practice. Some might suggest that given the thought, massive international observational study data and expert opinion that have contributed to the proposed fundamental change in our diagnostic approach to GDM, that it is too late to debate this question. We differ, agreeing with Joubert (1754–1824) that, "It is better to debate a question without settling it than to settle a question without debating it." To evaluate the strength of evidence for the newly proposed GDM diagnostic criteria, we reviewed the English language literature associated with GDM diagnosis (2008–2011) and found 81 related citations. Of these, 69% were opinions and 31% provided primary evidence derived from clinical studies (whether prospective or retrospective in nature and of any size and design). Furthermore, in the opinion group, 75% of the authors supported the newly suggested diagnostic criteria of the International Diabetes in Pregnancy Study Group (IADPSG) while 25% opposed it. By contrast, of the 31% clinical studies that included newly published data, 27% had conclusions that supported the new criteria, with 73% opposing it. These numbers suggest an uncomfortable paradox for our classification of research that is, opinions supersede the evidence of well-designed studies. Some authors contend that consensus statements and the opinions of "experts" should be the modus operandi of proposed new diagnostic or therapeutic criteria.[1–3] While reaching a consensus may ultimately improve care, basing consensus on questionable information may, in the long run, open Pandora's Box.[4] For a considerable amount of medical care, we are not always sure what really works. Even though diagnostic criteria rarely cause harm, the treatment we assign to the diagnosis may cause more harm than good and the patient, care provider and society pay for it in many ways. Perhaps the time has come to learn that diagnostic approaches will improve pregnancy outcome and at the same time minimize health-care costs that are already over-burdened. To begin to attain this goal, we need fewer opinions and consensus statements, less passionate reactions and public fanfare and more scientific data generated by research. We may then continue to argue about who pays for what, but maybe we will be closer to learning what's worth paying for.

There are major principles that justify the revision of any diagnostic test. Primarily, the disease needs to be categorized as an important health problem with a significant adverse outcome. The prevalence will be determined based on the association between selected glucose thresholds and meaningful clinical outcome measures that justify intervention. Justification to accept a higher prevalence will be based on the severity of the principal

outcome. For example, thresholds resulting in a high prevalence that identify and prevent potential stillbirth will be accepted while thresholds for large-for-gestational age (LGA) in which 70% of the cases are derived from nondiabetic pregnancies will be questionable.[5,6] Furthermore, the expenditures to accommodate the test would need to be economically balanced in relation to overall health-care costs.

ORAL GLUCOSE TOLERANCE TEST: REQUIREMENTS AND LIMITATIONS OF A DIAGNOSTIC TEST

Diagnostic tests differ from screening tests in that they are applied to patients with positive screening results and/or symptomatic populations. The definition of a clinical problem requires an understanding of what constitutes normality. For a clinical measure or test to be reliable, it must be able to distinguish between normal and abnormal values to identify those individuals who have already or will develop a pathological state. For a test to be considered clinically applicable, it must meet six criteria: (1) reproducibility, (2) precision, (3) simplicity (4) sensitivity, (5) specificity, and (6) cost-effectiveness.[7] The ultimate benefit of the diagnostic test lies in the care provider's ability to change the course of the disorder and reduce morbidity and mortality. The disease should have a prevalent and identifiable preclinical state during which diagnosis leads to improvement. The ideal diagnostic test for gestational diabetes has not yet been developed. There are limitations of the OGTT that include test duration, time of performance (morning only after nocturnal fast), patient discomfort, especially during the first trimester with potential nausea and vomiting as well as the supra-physiological glucose load unrelated to body weight. Finally, the issue of reproducibility remains a limitation.

REPRODUCIBILITY OF THE OGTT

Reproducibility was evaluated in multiple studies in pregnant and nonpregnant states. An increased variability was greater for pregnant versus nonpregnant women. When the values from two tests for reproducibility were compared, the least amount of variation was found in fasting plasma glucose 7–19 mg/dL and one-hour of 30–45 mg/dL. The lower the suggested criteria and number of abnormal values, the greater the potential for variability. The evidence has shown that the OGTT is not reproducible for diagnosis in 24% of cases when the NDDG criteria are used.[8,9] We do not as yet have evidence of the level of reproducibility of the IADPSG criteria. It may not always be cost-effective to implement the use of a new diagnostic technique when relatively minor improvements do not justify the added costs. Knowing the nonuniform nature of hospitals, private offices, and clinics, each will make the determination if to implement high-tech time-consuming solutions when low-cost, low-tech alternatives are effective and acceptable for patients' needs.

In nonpregnant individuals, repetition of the test showed a mean difference of 26 mg/dL at one-hour and 20 mg/dL at two-hour levels.[10] In a study of 32 women of whom 16 were GDM and 16 had normal glucose tolerance test (GTT) results at 31 weeks gestation, we demonstrated that when the women were retested within 10 days, there was 18% variability for the nondiabetic and 10% for the GDM women. Significant differences in the OGTT results, especially in the nondiabetic group, at a gestational age at which one would expect the greatest reliability, must be taken into consideration with high-risk patients (e.g., previous GDM, obesity) and retesting should be a major consideration.[11] Following our study, several investigators reported similar findings.[9] They found significant variability in the OGTT results especially when glucose values were in the upper normal range. This resulted in reclassification of many patients from nondiabetic to diabetic. Therefore, they recommended that borderline OGTT results be repeated. Espinosa de los Monteros et al. demonstrated that the reproducibility of the 50-g load was 90% for normal test results and 83% for abnormal results when the test was repeated the following day.[12] Catalano et al. reported that the OGTT was not reproducible for diagnosis in 24% (nine of 38) pregnant women.[8]

100 VERSUS 75-G GLUCOSE LOAD

There is no consensus on the glucose load concentration that needs be used for the glucose test. Several clinical studies have attempted to test if the 75-g load (recommended by the World Health Organization [WHO] and by the American Diabetes Association [ADA]) will be more convenient and provide greater accuracy than the 100-g load while others have suggested that some GDM women will not be identified with the lower load. The use of the 75-g load was first endorsed in 1997 by the Fourth International Workshop Conference on Gestational Diabetes[13] and was incorporated into the ADA Clinical Practice Recommendations.[14] This approach may be easier to tolerate by the patient (less nausea and vomiting), requires shorter testing time (three-hour determination eliminated) and is less expensive. Therefore, it is surprising that a survey conducted by Gabbe et al.[15] failed to show a sizeable percentage of physicians who use this diagnostic test routinely. The most commonly accepted method of diagnosis of GDM in the United States is the 100-g OGTT using the NDDG criteria.[16] The criteria has been continually endorsed by the American College of Obstetrics and Gynecology (ACOG), ADA and the Second, Third, and Fourth International Workshop Conferences on Gestational Diabetes.[17–22]

At no time during the diabetes, in pregnancy workshops or in institutional endorsements have the issues of hyperosmolarity of the glucose solution, delayed gastric emptying and associated patient nausea been addressed. We investigated the effect of different glucose loads, 50 versus 100 g, to gauge women's comfort and homogeneity on the OGTT curve. We used a modified more physiologic glucose solution that enhances more rapid gastric emptying and, therefore, a marked decrease in the incidence of nausea and vomiting. Our findings suggest that a modified, lower osmolar glucose solution empties rapidly from the stomach and results in a more homogeneous glucose curve; it facilitates glucose absorption into the peripheral circulation more smoothly.[23,24]

Today, with the 100-g load, physicians often obtain results in which the two-hour or three-hour results are greater than the one-hour. A common practice in these cases is to assume a lab error and to reassign the results according to the expected curve. This reversal can make a diabetic patient a nondiabetic one. Rather than reverse results to resolve the unexpected glucose pattern, patients and care providers should be aware that it is the hyperosmolar

solution and the delayed stomach emptying that are probably responsible for this phenomena.

A report by Mello et al.[25] suggested that more women meet the diagnostic threshold for GDM when the 100-g glucose is used in comparison to the 75-g load. We compared 75 and 100-g loads with each patient serving as her own control. Women were diagnosed with GDM with the 100-g load (NDDG criteria); 63% of them were categorized as non-GDM when the 75-g load was administered. In addition, 50% of the GDM patients when tested with the 75-g load had only one abnormal value. However, using the NDDG criteria with one or more abnormal values on the 75-g load resulted in identification of 90% of GDM patients.[26] In contrast, some investigators found that the lower load is beneficial.[27–29] Schmidt et al. in a large scale observational study (n = 4977) demonstrated that a 75-g glucose load identified women who were at risk for preeclampsia, delivery of a macrosomic infant and increased perinatal mortality. Their data confirmed that GDM is independently associated with fetal macrosomia and preeclampsia as previously described by Sacks and Sermer et al.[30] These studies demonstrated that GDM, independent of age, obesity, and other risk factors, predict perinatal mortality. For example, the adjusted (for age and obesity) relative risk for perinatal mortality in Schmidt's study was 3.1. However, these studies did not address how many of the GDM women (by the NDDG criteria) will remain undiagnosed with the 75-g load. Only after addressing the rate of misdiagnosed women can we make a determination of the most efficacious load.

OGTT: DIFFERENT DIAGNOSTIC THRESHOLDS

In preexisting diabetes, the level of glucose used for diagnosis is based on the risk for microvascular disease. For example, in recent years, the fasting plasma glucose threshold for diagnosis of overt diabetes was reduced from 140 mg/dL to 126mg/dL. Although this automatically increased the number of patients diagnosed (labeled) with diabetes, it also enhanced the possibility for earlier detection, intervention and potential for decreased morbidity. Similarly, the lower threshold of impaired fasting plasma glucose was changed from 115 mg/dL to 100 mg/dL to detect individuals at risk for metabolic syndrome. Plasma glucose is a more accurate measure than hemoglobin A1c (HbA1c) for diagnostic purposes since the coefficient of variation of glucose is 3% while that of HbA1c is 16.5%.[31] The use of HbA1c for the diagnosis of GDM is not currently recommended.[14,18,32]

In contrast to preexisting diabetes, the diagnostic criteria for GDM were based on long-term effects on the mother and only in the past decades has the association between OGTT thresholds and neonatal outcome been investigated. The original O'Sullivan criteria were based on the risk for developing type 2 diabetes rather than the risk for adverse pregnancy outcome. In 1964, O'Sullivan and Mahan[33] reported the results of a study of a three-hour oral 100-g GTT in 752 healthy pregnant women. Norms were established for whole blood during fasting, one-hour, two-hour, and three-hour values after glucose ingestion. The authors then followed a group of 1,013 women undergoing the OGTT during pregnancy and determined the incidence of adult onset diabetes in this population. After several years of follow-up, the cumulative incidence rate was 29% for women exhibiting OGTT values greater than two standard deviations during pregnancy. The authors suggested that pregnant women exhibiting this degree of carbohydrate intolerance during pregnancy be designated gestational diabetic. Subsequent follow-up of O'Sullivan's study population demonstrated that risk for the development of overt diabetes exceeds 50% within 15 years. More recent studies report the risk for subsequent diabetes may be as high as 15%–30% after two years of follow-up.[34]

Many diverse diagnostic criteria have been proposed throughout the world (Table 26-1). In 1990, at the Third International Workshop Conference on GDM, the consensus statement read: "Because it is hoped that international agreement will soon be reached as to appropriate and globally acceptable diagnostic criteria, it is advisable to introduce minor corrective modifications at present."[20] More than 20 years have passed; no international agreement has been reached and millions of women worldwide with a potential GDM diagnosis remain untreated and have suffered with the burdens of a degenerative disease.

The current diagnostic criteria for gestational diabetes in the United States were derived from the work of O'Sullivan and Mahan. The NDDG accepted and then converted the O'Sullivan criterion by applying a factor of 1.14 to convert whole blood to plasma thus creating the glucose thresholds known as the NDDG criteria. These criteria are the most widely used in the United States (approximately 56%) by obstetricians.[15] Carpenter and Coustan (C&C)[35] suggested an additional modification of the O'Sullivan criteria. This modification incorporates the change in the substrate and method used. The NDDG criteria did not correct for the reducing substances that are no longer measured in current laboratory procedures. The Somogy–Nelson technique uses whole blood and identifies other reducing substances in addition to glucose. Today, newer techniques measuring glucose oxidase or hexokinase are specific to glucose. Therefore, in addition to the change from whole blood to plasma (14%), the C& criteria subtracted 5 mg from the threshold created by the original conversion and rounded out the results. These criteria are used by approximately 33% of the obstetricians in the United States.

Using a mathematical model, Sacks et al.[36] studied the OGTT results of 994 pregnant women. The samples were tested with the Somogy–Nelson technique for whole blood and glucose oxidase for plasma. The study demonstrated that the Somogy–Nelson technique results in 2–6 mg higher values due to the presence of reducing substances. The diagnostic thresholds derived from the study were lower than those in the C&C study. The C&C and NDDG criteria were further compared with a prospective observational outcome study of 3,778 women aged 24 or older.[37] All subjects were subjected to the OGTT regardless of the screening results. One hundred and forty-three women met the criteria for gestational diabetes by the NDDG and received treatment. Care providers were blinded to the OGTT results of the remaining subjects. Of these, 115 subjects were identified as GDM using the C&Cr criteria. Similar rates of GDM (NDDG 3.9% vs. C&C 3.2%) were found although it would have been reasonable to assume that the lower threshold criteria would have resulted in a higher prevalence. Comparison between the untreated (C&C) and the treated GDM subjects revealed an increased risk for macrosomia (28.7% vs. 13.7% $P < .001$) and cesarean delivery (29.6% vs. 20.2% $P < .02$). In addition, the author found a twofold increased risk for cesarean delivery for the treated GDM women. This can be explained by the physician's knowledge of the existence

TABLE 26-1 Varying Criteria of Gestational Diabetes

	Fasting mmol/L	*1 Hour mmol/L*	*2 Hours mmol/L*	*3 Hours mmol/L*	*Values#*	*Load*	**Comment**
NDDG	5.8	10.6	9.2	8.1	2	100	Risks of GDM
C&C	5.3	10	8.6	7.8	2	100	Conversion of Factor
Sacks	5.3	9.6	8.4	7.3	2	100	Mathematical Conversion
Langer (NDDG)	5.8	10.6	9.2	8.1	1	100	Randomized
United Kingdom	8.0	—	11	—	1	75	Consensus
IADPSG	5.1	10.0	8.5	—	1	75	Consensus
Australia	5.5	8.0	1	1	2	75	Consensus
Canada	5.3	10.6	8.9	—	2	75	Consensus
WHO	7.0	—	7.8	—	2	75	Consensus
4th International	5.3	10	8.6	—	2	75	Consensus

Langer, one or more abnormal value based on NDDG criteria.
To convert to mmol/L to mg % multiple by 18.

of disease; this knowledge often becomes a self-fulfilling prophecy to deliver by cesarean section. The study may also support the idea that even the lower threshold criteria is associated with a higher rate of macrosomia compared to the general population.

THE OGTT ONE-ABNORMAL VALUE: PREDICTIVE VALUE, PATHOPHYSIOLOGY, AND GLUCOSE ABNORMALITY FOR A GDM DIAGNOSIS

Several investigators in the mid-80s proposed that glucose is a continuum and even relatively mild hyperglycemia is associated with adverse outcome in pregnancy. The majority of these studies used LGA or macrosomia as the outcome measure. Tallarigo et al.[38] found that even limited degrees of maternal hyperglycemia on the OGTT results within the normal range were associated with a significant increase in the rate of macrosomia, congenital anomalies, preeclampsia, and cesarean delivery. Similar findings were recently demonstrated.[39,40]

To make the determination if a condition is a disease, three criteria must be met: the presence of a significant adverse pregnancy outcome, pathophysiology that explains the condition, that is, GDM, and the availability of a treatment modality to mitigate the outcome. The concept that one abnormal value on the OGTT is sufficient for the diagnosis of gestational diabetes was proposed in the 1980s in retrospective, prospective, and randomized studies. In a case-controlled study, gravid subjects with untreated one abnormal value were compared to treated gestational diabetics and nondiabetic women. We reported a significantly higher rate of fetal macrosomia and metabolic complications in the untreated (one abnormal group) and a similar rate for nondiabetic and treated GDM subjects.[42] In another study,[42] we randomized gravidas with one abnormal value on the OGTT into treatment and nontreatment groups. The treatment group had a significant reduction in

adverse pregnancy outcome. Furthermore, the untreated group had higher rates of hypoglycemia (13 vs.2%, $P < .02$); polycythemia (14 vs. 2%, $P < .02$); and, LGA infants (24 vs. 6%, $P < .03$), respectively (Figure 26-3). Leikin et al. and Lindsay et al. concurred with our findings.[43,44] Leikin showed that patients with elevated screening tests but normal GTT results had an increased risk for delivering a macrosomic infant. Lindsay et al. reported a relationship between one abnormal value on the OGTT and pregnancy complications. Similar findings were reported by several other authors.[45–47] The results of these studies demonstrated that there is an adverse influence of even one abnormal GTT value on pregnancy outcome. Finally, it was demonstrated that patients with one abnormal value on the GTT by the C&C criteria when retested four weeks later, 34% were found to have two or more abnormal values on the OGTT results.[48]

The multiple criteria for diagnosis have resulted in different rates of prevalence even within the same geographic and demographic catchments. As a rule of thumb, the lower the thresholds (one abnormal value or glucose), the higher the prevalence. For example, a clinical evaluation of the two sets of criteria in 103 patients found that 10 of 39 (26%) patients whose GTTs were abnormal by the C&C criteria but not by the NDDG criteria required insulin during pregnancy.[48] This is a substantial number compared with the 20/65 patients (30%) who met only the higher NDDG criterion and suggests that the higher thresholds are not sensitive enough. In our own data, we found that over 70% of women who had one abnormal value using the NDDG criteria had two or more abnormal values when their results were applied to the C&C criteria. Again, this demonstrates that one abnormal value is indicative of disease and that it should be treated as such. Timely identification and treatment will result in improved perinatal outcome.

Furthermore, the studies demonstrated that untreated women with one abnormal OGTT values are at two- to threefold higher risk compared to treated subjects. In a large cohort of women ($n = 89{,}141$), the two-step procedure supported the use of isolated abnormal fasting value based on the IADPSG with odds ratio for LGA of 1.89, 95th confidence interval, 1.45–2.45.[49] In addition, it was shown that adverse pregnancy outcome and glucose characteristics are similar in women with 1, 2, and even 3 abnormal values on the OGTT.[50] When patients with one abnormal value were compared to GDM (equal or greater than two abnormal values), both groups had similar rates of neonatal metabolic syndrome (20% vs. 18%).[51]

GLUCOSE PROFILE AND PATHOPHYSIOLOGY

In an attempt to determine the ambulatory metabolic control of subjects ($n = 126$) with one abnormal, or two or more abnormal values (before and after treatment) and nondiabetic women, we used the Ambulatory Glucose Profile.[41,52] Glucose profiles from women with either two or more abnormal values or one abnormal value were comparable. In another study of 36 women with one abnormal value and 29 nondiabetic controls, we used the Bergman Minimal Modeling Method that provides a means to assess insulin sensitivity and β-cell function in vivo. We demonstrated that 66% of women with one abnormal value on the OGTT had an insulin sensitivity response below the nondiabetic fit curve. Finally, in the one abnormal group, obese subjects had lower sensitivity than lean subjects. (Figures 26-1 and 26-2) and those with two or more abnormal values (C&C criteria). Furthermore, 80% of low responders exhibited abnormal findings postpartum.[53,54] Similar findings in other studies showed that fasting insulin and insulin resistance were indistinguishable in patients with one abnormal value or GDM. Moreover, higher insulin levels and greater insulin to glucose ratios, a reflection of insulin resistance, was identified in these "normal" gravidas.[55] Recently, it was reported that …" like GDM, isolated one-hour hyperglycemia on the OGTT is associated with β-cell function and increased risk for LGA neonates.[56,57] They reported that women with one abnormal glucose test value have an increased risk for fetal obesity, hyperinsulinemia, postpartum hypoglycemia, and placental immaturity.

The current findings of the existence of pathophysiology in women with one abnormal value and the existence of increased

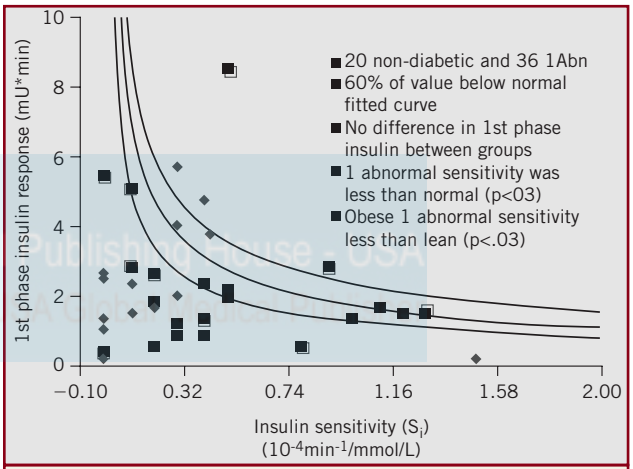

Figure 26-1 Abnormal Value: Antepartum Pathophysiology.

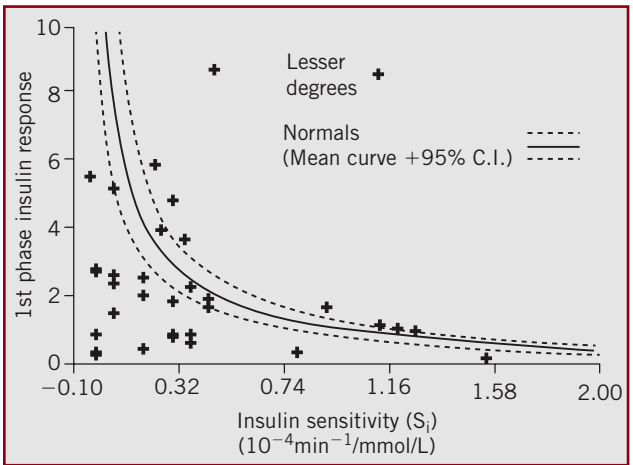

Figure 26-2 Pathogenesis of Subjects Lesser Degree of Glucose Abnormality.

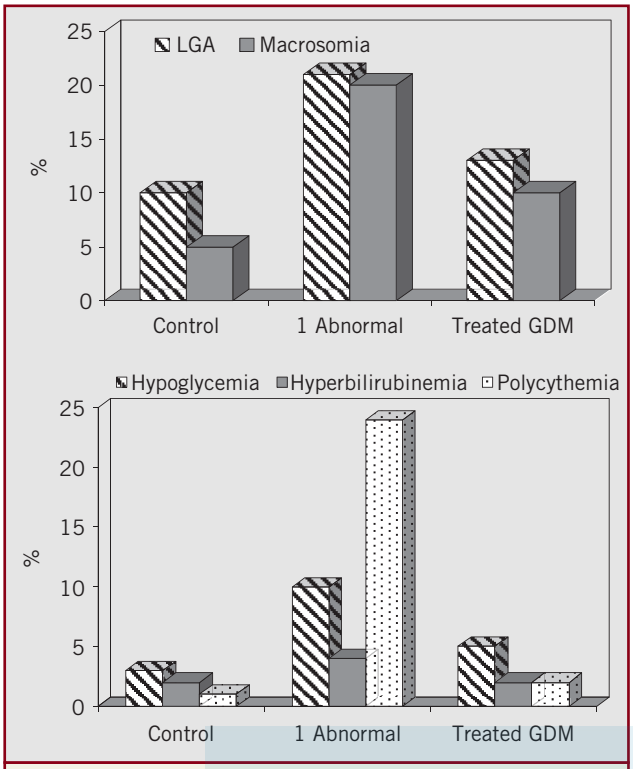

Figure 26-3 The Incidence of Adverse Neonatal Outcome.

adverse outcome of pregnancy supports the recommendation of the IADPSG criteria[58] endorsed by the ADA. However, we need to observe caution since the impact of one abnormal value on the prevalence by the suggested criteria remains unknown. Furthermore, there is paucity of information on the benefit of treatment of these patients diagnosed using one abnormal under the IADPSG criteria. The impact on outcome may be relatively small while the impact on the prevalence may be the reverse with an unsupported cost-benefit formula. On the other hand, we suggest that these data are much stronger in supporting the change and that the similarity in pathophysiology and outcome suggest that treatment should be similar.

THE CURRENT DEBATE AND WHERE ARE WE HEADED

To alter the current diagnostic criteria to conform to the IADPSG proposal, several distinct unknowns and areas of difference need to be addressed.

1. Which clinical outcomes do we seek to improve and how will we measure them?
2. Do we adopt a one-or (sequential) two-step screening strategy?
3. Should the GDM diagnosis be based on a single abnormal value or require two or more abnormal values?
4. Is there justification to lower the OGTT glucose threshold?
5. Should we be concerned if different populations of women exhibit markedly varying GDM prevalence due to adoption of new diagnostic criteria?
6. Should we consider cost-benefit and resource allocation implications of increased GDM prevalence as consequences of broadened diagnosis?

The Fourth International Workshop on Gestational Diabetes[13] supported by the ADA and the ACOG attempted to decrease controversy surrounding screening and diagnosis of gestational diabetes. It recommended that both the C&C and NDDG criteria be used for diagnosis of GDM in either a one or a two-step approach. The recommendation of the conference participants did not produce a definitive diagnostic protocol but instead endorsed approaches for diagnosis, the 100-g and 75-g oral glucose loads using the C&C threshold.

ONE-STEP APPROACH

The one-step approach uses the 75-g load (popular in Europe) with the threshold suggested by the C&C criteria (fasting 95 mg/dL, one-hour 180 mg/dL, two-hour 155 mg/dL); it eliminates the three-hour sample and relies on two or more abnormal values for diagnosis. It is performed without prior plasma or serum glucose screening. This approach may also be cost-effective for high-risk patients. This consensus was a significant change from the traditional WHO criteria (Table 26-2).

TWO-STEP APPROACH

This model recommends using universal or selective screening with an initial 50-g oral glucose load (glucose challenge test [GCT]). The glucose thresholds that are used as positive test results are still not universally accepted and range from 130 mg/dL to 140 mg/dL (see Chapter 25). A positive screening result should be followed by the traditional OGTT as recommended by the NDDG or C&C criteria (Table 26-3) (Figure 26-4). The Consensus statement, instead of creating consensus has left us with universal versus selective screening and at least three different diagnostic criteria for gestational diabetes. This lack of uniformity precludes comparison and with multiple criteria results in different patient populations being designated GDM.

TABLE 26-2 One-Step Approach for Diagnosis

Perform OGTT without prior plasma or serum glucose screening
May be cost effective in high-risk patients
Diagnosis of GDM with a 75-g oral glucose load

	Mg/dL	mmol/L
Fasting	95	5.3
1-h	180	10.0
2-h	155	8.6

The National Institutes of Health (NIH) consensus statements present up-to-date research on a particular topic followed by open discussion of the merits of each argument. Thus, these consensus statements represent the findings and opinions of the conference participants and *not* those of the NIH. The primary mission of the NIH is research; it does not give specific, detailed practice algorithms. Nevertheless, its consensus statements are widely read and have the potential to have immediate clinical impact, if properly timed.

TABLE 26-3 Two-Step Approach of Diagnosis

Initial 50-g oral glucose load (GCT)
Perform a diagnostic OGTT for women exceeding the glucose threshold value on the GCT
Diagnosis of GDM with 100-g Oral Glucose Load

	C & C	NDDG[a]
Fasting	95	105
1-h	180	190
2-h	155	165
3-h	140	145

Two or more abnormal values.
[a]One of more abnormal values.

Currently, two schools of thought have emerged regarding the diagnostic criteria. One methodology supports the one-step approach and change in the diagnostic threshold, that is, IADPSG.[58] The second approach recommended by ACOG, the NIH Consensus Conference and several experts[21,22,59,60] seek to maintain the two-step approach with the current criteria for diagnosis. The National Institute of Child Health and Human Development (NICHD) and the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) studies and Landon et al.[61,62] helped us to determine the lower end of the hyperglycemic spectrum that should be considered GDM and define the rate of morbidity in this subset of women. However, neither study addressed the question of the magnitude of the adverse perinatal outcome in all disease severity levels of the spectrum since they a priori excluded women who would have been candidates for pharmacological therapy with either fasting plasma glucose of >95 mg/dL (NICHD) or >105 mg/dL (HAPO). Another two studies shed light on the association between the GDM severity spectrum of GDM and morbidity.[63]

The reason to apply lower glycemic thresholds for the interpretation of OGTT results is not surprising when one evaluates

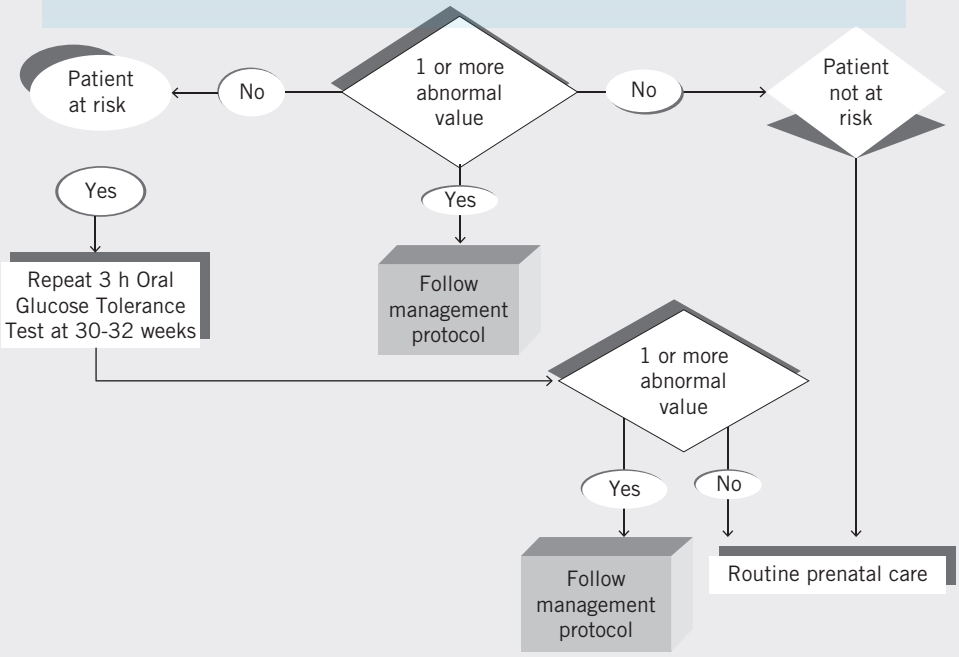

Figure 26-4 Management of Oral Glucose Tolerance Test.

the history of the GTT as a diagnostic instrument for GDM. The diverse prevalence reported from different countries or even centers within the United States are, in part, the result of different criteria. A diagnosis of normal in one area reverts to diabetic in another. The intensity of screening of patients at risk for the disease will affect the prevalence of the disease in a given population.

The prevalence of GDM ranges from 4%–6% in the United States. In fact, the majority of reported studies in the past decade demonstrated a significant increase in the rate of GDM in relation to different diagnostic criteria thereby altering the resulting prevalence of GDM. In a recent study of 4,659 women, comparing the NDDG to the C&C criteria demonstrated that the prevalence of GDM was 3.3% with the NDDG and 4.6% with the C&C standard. This represents a 30%–50% increase in the number of women who are labeled diabetic.[64,65] In a study by Gokcel et al.[66] the prevalence of GDM was 6.5% using the C&C criteria and 4.1% using the NDDG. In Taiwan, the incidence of GDM was 3.5% using the NDDG and increased to 7.9% using the C&C criteria. The authors concluded that in their target population, using the C&C criteria showed no benefits over using NDDG criteria.[67] In Turkey, a comparison study revealed a prevalence of 8.1% with the C&C criteria and 5.6% using the NDDG criteria.[68] Some authors have even suggested ethnic-specific guidelines for GDM diagnosis.[69]

The contributing factors to GDM prevalence include obesity, racial, ethnic disparities, and the threshold used for diagnosis. Each incremental modification in the threshold criteria can potentially elevate or lower the disease prevalence. An increased prevalence of about 3% occurred when the C&C criteria substituted the NDDG standard. Using the IADPSG criteria will result in an 18% increased prevalence. Even the frequency of GDM at the various HAPO testing centers using the IADPSG consensus showed substantial center-to-center variation with a range of 9.3%–25.5% with an overall prevalence of 17.8%.[70,71] For varying regions of the world, similar findings, using the new proposed criteria found a prevalence ranging from 12.4%–37.7%.

The new criteria have not extended the options available for GDM diagnosis; they have, however, raised the issue that given the regional differences, can a single, uniform criteria adequately identify GDM and at what cost? Is there justification for substituting GDM diagnosis with the new criteria with the knowledge that any decrease in the threshold will result in an increased prevalence of 18% or more with the accompanying social and economic burden? There have been no adequately designed and powered randomized studies to answer the question if new diagnostic criteria as recommended by the IADPSG consensus will clinically, socially, and economically be efficient and effective. The medical model does not exist in a cultural vacuum. The social nature of illness is particularly evident with the application of a medical label, that is, GDM. When a woman is identified with an expensive or feared medical condition, it significantly disrupts her life and often increases her psychological stress. The experience of being labeled "sick" has both short- and long-term social as well as physical consequences.[72–74]

If the new IADPSG criteria, one-step diagnostic test, using one-abnormal value on the OGTT are implemented, the result will be a significant increase in patient volume. Hospitals, clinics, and private physician offices will now need to determine how to deploy and manage personnel and space. Access to enhanced testing may lead to greater demands on staff as productivity rises and more is expected of them. How many more doctors, nurses, diabetic nurse educators, clerks, and so forth will need to be employed to accommodate the increased number of patients that will now be screened and diagnosed? How will current physical facilities address the issue of enhanced allocation of space to accommodate greater patient volume needing testing? Will current laboratories be able to accurately and efficiently handle the increased volume? These are just a few of the decisions that will need to be made[59,60,75–77]

New diagnostic criteria should be selected with the patient in mind. It should be easy to test and pose minimal invasion to the other areas of her life. A patient may be willing to test but may not be able to test because of familial (i.e., child care) or employment commitments. The employed patient who needs to test early in the morning will generally forgo returning to work that day. The number of work days lost to testing multiplied by the millions of pregnant women in the USA will impose an additional economic burden to the already overburdened health-care system.[78–80] Recent studies evaluating the cost-effectiveness of the one-step method recommended by the IADPSG and the two-step currently used in many institutions worldwide have shown that the two-step approach will be more cost efficient. A single study found that the one-step approach will be more beneficial but only when postpartum counseling and care were included. When the postpartum component was not part of the provision of care, there was no difference in the diagnostic approaches.[81–83]

POSTPARTUM EVALUATION OF THE GDM PATIENT

GDM does not end with the birth of the child. On the contrary, for many mothers it may be the onset of a chronic disease. Glucose homeostasis and insulin sensitivity appear to change within the first few days postpartum. These changes may be the result of diet, enhanced activity, and onset of lactation and decreased placental hormones. Several investigators have reported a decrease in fasting plasma insulin levels two days postpartum while fasting plasma glucose levels increased. These changes may last 5–6 weeks after delivery while the glucose metabolism stabilizes.[84,85] About 30% of GDM women may have diabetes or prediabetes postpartum. Depending on ethnicity and other risk factors for a given population, the incidence of undiagnosed type 2 diabetes ranges from 9%–15%.[86–89] Furthermore, a significant number of the GDM women will be classified as impaired glucose tolerant. In our own data of 5,000 OGTT results performed during pregnancy in GDM patients, after correcting for the 10 mg physiological decrease of fasting plasma during pregnancy, approximately 70% will have fasting plasma results >100 mg/dL that classifies them as impaired fasting glucose (Table 26-4). However,

TABLE 26-4 Criteria for the Diagnosis of Diabetes Mellitus

Nondiabetica[a]	CTR[a]	Diabetes[a]
FPG		
>100	>100 < 126	>126
2-h PP		
<140	>140 < 200	>200
		Symptoms of DM
		And casual plasma
		Glucose > 200 mg/dL

Abbreviations: DM, diabetes mellitus; FPG, fasting plasma glucose; IGT, impaired glucose tolerance.
Diagnosis confirmed on a subsequent day.
[a]mg/dL.

only about half are tested and even fewer are tested 6–12 weeks postpartum.

Timely testing for prediabetes may provide an opportunity for care providers to prevent or delay the onset of type 2 diabetes through diet, physical activity, weight management, and pharmacological therapy. ACOG and the ADA currently recommend testing women with a history of GDM 6–12 weeks postpartum. If the test results are normal, they recommend retesting every three years and at the first prenatal visit in a subsequent pregnancy. If prediabetes is diagnosed, the test should be administered annually (Figure 26-5).[90,91]

SUMMARY

Gestational diabetes is characterized by a decrease in insulin secretion and/or increase in insulin resistance. This is true in all disease severity levels (from one abnormal to four abnormal values). Early diagnosis will result in a significant improvement in perinatal outcome. The method of diagnosis (one- or two-step approach) is of less importance. Although multiple thresholds have been suggested for diagnosis, their practical value is limited since the differences are minimal. However, the lower the threshold, the higher the prevalence of the disease and the greater the number of women committed to treatment. We need to press the pause button. Rather than moving forward into as yet not fully vetted criteria, we have a moral responsibility to encourage empirical research that will maximize certainty, consistency, and predictability. Our standard needs to be: do not block the road to inquiry and repeatedly address the questions of why and how.

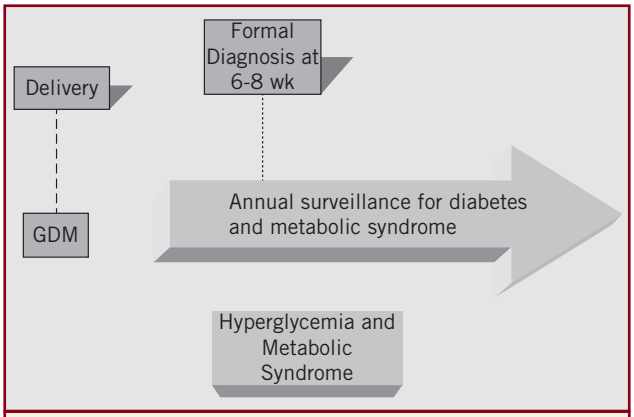

Figure 26-5 Post Pregnancy: Surveillance for Type 2 Diabetes Impaired glucose tolerance or Metabolic Syndrome.

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Oral Antidiabetic Agents in Pregnancy: Their Time Has Come

27

Oded Langer, MD, PhD

Discovery consists of seeing what everyone has seen AND
Thinking what nobody has thought.

—Albert von Szent Gyorg

Key Points

- Glyburide, possibly metformin, and insulin are equally effective for gestational diabetes mellitus (GDM) treatment at all disease severity levels
- Reserve medical therapy with oral agents for patients whose fasting plasma glucose levels remain above 95 mg/dL (or postprandial levels above 120 mg/dL) despite diet therapy
- Level of glycemic control achieved, not the mode of therapy, is the key to improving outcomes in GDM pregnancy
- Combination therapy with addition of 1–2 oral agents or insulin is appropriate
- Medication is just one component of intensive therapy
- Well-designed studies report no association between oral agents and congenital malformations
- Oral agents and insulin minimally cross the placenta without causing harm
- Glyburide and insulin should be used as the first-line drug for obese diabetic women

INTRODUCTION

GDM continues to be a major public health problem for the mother and unborn fetus with an estimated incidence of 3%–20%, depending upon diagnosis criteria and geographic location affecting at least 150,000–550,000 women annually in the United States. Both type 2 diabetes and GDM are heterogeneous disorders whose pathophysiology is characterized by peripheral insulin resistance, impaired regulation of hepatic glucose production, and declining β-cell function. The use of oral antidiabetic agents in nonpregnant type 2 diabetes because of convenience of administration and inexpensive cost relative to insulin has become the standard of care in the United States to help patients maintain the targeted level of glucose control that lowers risk for microvascular complications.

The use of oral agents in pregnancy was historically contraindicated, but their use has increased over time; from 2001 to 2007, the use of these agents has increased threefold. This increase was the result of increased use of metformin already during the first trimester for PCO patients and the use of glyburide and metformin during the second and third trimesters.[1] Although the American College of Obstetricians and Gynecologists in the past did not recommend oral hypoglycemic agents (OHAs), the Practice Bulletin of the American College of Obstetrics and Gynecology stated that when pharmacological therapy for GDM is indicated, insulin and oral medications are comparable in effectiveness and either can be appropriate treatment modalities.[2] Because of new and refined studies in the literature, the majority of experts in the United States in both review and editorial articles have begun to endorse the use of glyburide (sulfonylurea) as an alternative pharmacological therapy to insulin.[3–6] Gabbe et al.[7] stated "… an alternative to insulin therapy is the oral hypoglycemic agent glyburide.… In our experience glyburide has become the first choice for patients with GDM who require therapy beyond diet." Saade[5] in 2005, in an editorial in *Obstetrics/Gynecology* stated: "Given the available evidence, glyburide is a reasonable alternative to insulin therapy in many pregnant women with GDM who do not achieve glycemic control with diet alone."

This recommendation was endorsed although it has not yet been approved by the U.S. Food and Drug Administration. Drug therapies have historically had to play catch-up to current research evidence. In addition, they have been subject to political,

financial, and policy considerations made by esteemed forums and drug manufacturers. Therefore, their use may swing from one end of the continuum to the other. The cornerstone of treatment is diabetic diet and when dietary modifications fail to control the elevated maternal glucose level, pharmacological therapy is initiated. Additional drug support with oral agents or insulin will be required in 20%–60% of pregnancies compromised by gestational diabetes.[8]

The objectives of glycemic control are to avoid maternal and fetal complications to enhance positive pregnancy outcome. The subject of OHA in pregnancy is replete with more opinions than evidence-based data. In a review of the literature, we found that 67% of the articles represented opinions (meta-analysis, editorial reviews, and literature reviews) while 20% were composed of clinical studies with placental transfer studies an additional 13% (Figure 27-1). Therefore, we need to clearly formulate the questions before we start looking for answers:

Do oral agents (e.g., glyburide) affect progression to type 2 diabetes later in life after women were treated during pregnancy?

Do oral antidiabetic drugs preserve or restore β-cell function in pregnancy?

What are the pharmacokinetic and pharmacodynamic considerations?

Which antidiabetic drugs cross the placenta and if they cross, what are the effects on the fetus?

Do hypoglycemia and the rate of fetal anomalies increase during glyburide therapy?

Which are the most effective treatment modalities for women with GDM?

At all levels of the GDM severity spectrum, is there a difference between pharmacological therapies?

How is selection of pharmacological therapy influenced by maternal weight?

How does each of the drug therapies affect lactation?

Which pharmaceutical modality is most cost effective?

"…no form of mild diabetes exists, and no excuse exists to postpone appropriate and effective treatment."[9]

The characteristics of currently available glucose-lowering interventions, when used as monotherapy, are summarized in Table 27-1. The glucose-lowering effectiveness of specific modalities and combination therapies demonstrated in clinical trials are the result of not only the essential characteristics of the intercession but also on the duration of diabetes, baseline glycemia, previous therapy, and other factors. A key feature in the selection of a medication to initiate or alter therapy is the ambient level of glycemic control.[10] It should be noted that glycemic thresholds in pregnancy are lower than those in the nonpregnant state. Therefore, drugs that are effective in nonpregnancy will fail to achieve the desired level of control in pregnancy. For example, a type 2 diabetic or GDM woman with hemoglobin A1c (HbA1c) of 8%–9% will fail to achieve the targeted level for pregnancy (see chapter on glycemic thresholds). Obviously, the choice of glycemic goals and the medications used to achieve them must be individualized for each patient and each potential pregnancy complication that we aim to prevent. The selection of the appropriate drug therapy is predicated on safety issues, side effects, tolerability, ease of use, long-term adherence, and cost.

DO ORAL AGENTS (E.G., GLYBURIDE) AFFECT PROGRESSION TO TYPE 2 DIABETES LATER IN LIFE IN WOMEN TREATED DURING PREGNANCY? DO ORAL ANTIDIABETIC DRUGS PRESERVE OR RESTORE β-CELL FUNCTION IN PREGNANCY?

The use and efficacy of sulfonylureas and metformin in the treatment of nonpregnant type 2 diabetes is well established.[11]

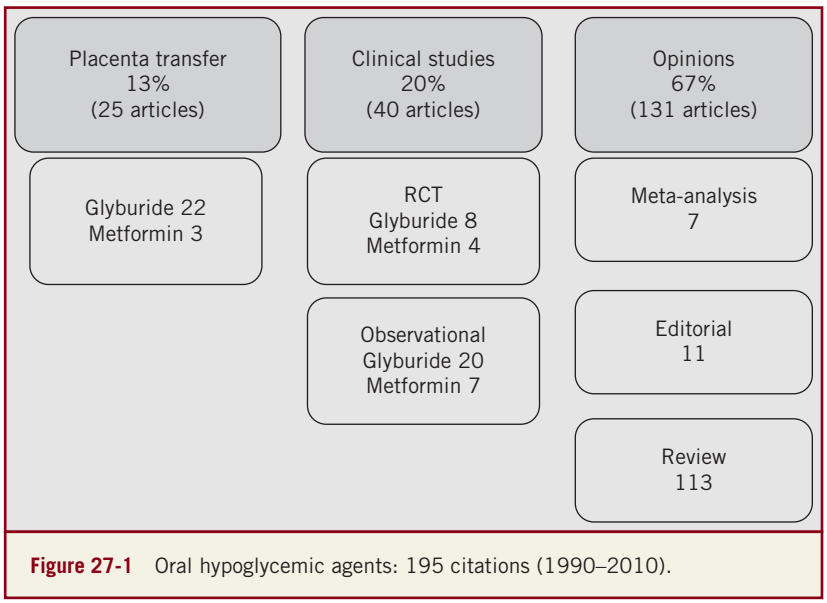

Figure 27-1 Oral hypoglycemic agents: 195 citations (1990–2010).

TABLE 27-1 Oral Antidiabetic Drugs: Classification

Drug	Mechanism of Action	Pregnancy Category	Decrease in FPG (mg/dL)	Decrease in Hb A1c (%)	Cross Placenta	Excreted in Breast Milk
Sulfonylureas	Increase insulin		60–70	1.5–2		
Glimepiride (Amaryl)	Secretion	C			Unknown	Unknown
Glipizide (Glucotrol)		C			Minimal	Unknown
Glipizide-GITS (Glucotrol XL)		–			–	–
Glyburide (DiaBeta, Glynase, Micronase)		B			Minimal	No
Meglitinides	Increase insulin		9–21	0.5–0.8		
Nateglinide (Starlix)	secretion	C			Unknown	Unknown
Repaglinide (Prandin)		C			Unknown	Unknown
Biguanide	Decreases hepatic	B	59–78	0.9–2	Yes	No
Metformin (Glucophage)	gluconeogenesis; increase insulin sensitivity					
Glitazones	Increased insulin		59–80	1.4–2.6		
Pioglitazone (Actos)	sensitivity; decrease	C			Unknown	Animals
Rosiglitazone (Avandia)	hepatic glucose production	C			Minimal	Animals
α-Glucosidase inhibitors	Slow absorption of		20–30	0.5–1		
Acarbose (Precose)	carbohydrates in the	B			Unknown	Animals
Miglitol (Glyset)	intestine	B			Unknown	Animals

Abbreviations: FPG, fasting plasma glucose; GITS, gastrointestinal therapeutic system.

The primary effect of sulfonylurea drugs is to enhance insulin secretion.[12,13] Studies have demonstrated that these drugs can also enhance peripheral tissue sensitivity to insulin.[14,15] Since β-cell exhaustion plays an important role in the development of overt diabetes and insulin resistance is a characteristic feature of type 2 diabetes and GDM, it follows that the use of a sulfonylurea agent may be beneficial in the prevention of GDM complications in high-risk populations. GDM is diagnosed late in the second trimester and patients are delivered close to the 38–39th weeks gestation. Thus, the interval between diagnosis and delivery is relatively short. If 8–12 weeks of treatment permanently caused the deterioration of pancreatic function, then it would logically follow that oral agents would not be administered in the daily regimen of type 2 diabetics. Insulin deficiency is a progressive condition that is not adversely affected when patients receive sulfonylurea, metformin, or insulin.[11,16–18]

It is clear from the United Kingdom Prospective Diabetes Study (UKPDS) and other epidemiological studies that treatment with antidiabetic drugs such as metformin, glyburide, and thiazolidinedione (TZD) and possibly other agents may preserve β-cell function to some extent, but we do not yet know how effective they may be in the long run. Thus, sulfonylureas and metformin have no lifetime protective effect on the β-cells deterioration and cardiovascular complications. Many factors contribute to the rate of β -cell deterioration (obesity, level of glycemic control, etc.) and progressive decline in β-cell function. By approximately three years, 50% of patients required the addition of a second agent to enhance glycemic control.[19]

Insulin secretion in response to glucose stimulation characteristically has two components. The first-phase rapid insulin release occurs within the first 5–10 minutes and is followed by more prolonged sustained insulin release referred to as second-phase insulin secretion. In type 2 diabetes and probably gestational diabetes, this normal physiology of insulin secretion is disrupted early in the development of the metabolic abnormality. Characteristically, the first phase is the first to be lost. In GDM, opinions differ if the first phase is lost, decreased, or remains unchanged as in nondiabetic individuals. A decrease in the first phase of insulin should not be equated with an automatic decrease in cell mass. It may be that there is a sufficient amount of β-cell mass but their function has been impaired. The β-cell becomes "blinded" to the stimulatory effect of the glucose. This glucose toxicity can be decreased with the use of antidiabetic drugs. Therefore, the relatively short time that an antidiabetic drug, that is, glyburide is used in pregnancy (between 8 and 28 weeks) in comparison to the number of years of use in the nonpregnant state reported in many studies, suggests no negative effect on the mother's pancreas, that is, β-cells. Thus, by decreasing the glucose toxicity, the result may be a decreased exhaustion of β-cells during pregnancy.

WHAT ARE THE PHARMACOKINETIC AND PHARMACODYNAMIC CONSIDERATIONS?

OHA: Classification and Characteristics

The prevalence of type 2 and gestational diabetes has increased by 33% in the last decade in the United States.[2] This is attributable to the increased rate of obesity in the general population in all ethnic groups and the trend toward advanced maternal age in pregnancy. Because of the relative ease of administration and low cost involved in overall therapy with oral agents, they have become

the drug of choice in the treatment of type 2 diabetes. One can assume that their popularity will only increase in the future especially after confirmation from the UKPDS of nonpregnant type 2 patients.[16] The study demonstrated that intensified versus conventionally treated patients use of sulfonylureas/insulin resulted in a decrease of 26% of microvascular complications, 21% in progression of retinopathy (during 12 years), 34% decrease in microalbuminuria, 16% in reduction in myocardial infarction, and 10% in diabetes-related deaths. Our randomized study of the use of OHAs demonstrated that glyburide is an efficacious alternative to insulin in the treatment of diabetes in pregnancy.[20]

Antidiabetic Drugs: Classification and Mechanism of Action

The oral hypoglycemic and antihyperglycemic agents act, depending upon the specific group, directly upon the β-cells to increase insulin secretion, and/or to decrease hepatic glucose production and increase peripheral insulin sensitivity. The advantages of using these agents rather than administering exogenous insulin are patient comfort and convenience with comparable effects on pregnancy outcome (Table 27-1).

Sulfonylureas

Clinical trials led to the discovery of tolbutamide in the 1950s and since then many agents in this class of drugs have been developed such as chlorpropamide. Second-generation sulfonylureas today include drugs such as glyburide and glipizide. In 1997, the first drug in a new class of oral insulin secretagogues called meglitinides (benzoid acid derivatives) was approved for clinical use. The agent repaglinide gained acceptance as a fast-acting, premeal therapy to limit postprandial hyperglycemia.[21]

Sulfonylureas bind to specific receptors on β-cells, forcing closure of potassium adenosine triphosphate (ATP) channels and opening the calcium channels that cause an increase in intracellular calcium that stimulates insulin release. The major effect of these drugs is to enhance insulin secretion.[12,15,22] These drugs may also increase insulin levels by reducing hepatic clearance of the hormone, the main contributor to fasting hyperglycemia. Enhanced insulin secretion diminishes glucose toxicity and improves insulin secretion after meals thus reducing postprandial hyperglycemia. These drugs can also enhance peripheral tissue sensitivity to insulin.[14,15]

The major adverse side effect is hypoglycemia, which can be prolonged and life threatening, but such episodes, characterized by a need for assistance, coma, or seizure are infrequent. However, severe episodes are relatively more frequent in the elderly. Chlorpropamide and glibenclamide (known as glyburide in the United States and Canada) are associated with a substantially greater risk of hypoglycemia than other second-generation sulfonylureas (gliclazide, glimepiride, glipizide, and their extended formulations), which are preferable.[23,24] In addition, weight gain of approximately 2 kg is common following the initiation of sulfonylurea therapy. Although the onset of the glucose-lowering effect of sulfonylurea monotherapy is relatively rapid compared with, for example, the TZDs, maintenance of glycemic targets over time is not as effective as monotherapy with a TZD or metformin.[25] Concerns were raised that sulfonylureas, as a drug class, may increase cardiovascular disease (CVD) mortality in type 2 diabetes; they were not substantiated by the results of the UKPDS or ADVANCE studies.[26,27]

The mechanism of action of sulfonylureas is to rapidly facilitate insulin secretion in response to nutritional intake that will result in minimal to no lag time between the changes in plasma glucose and modification of the insulin secretory rate.[28,29] This occurs in direct proportion to plasma glucose levels from 60 to 180 mg/dL. On the other hand, sulfonylureas do not stimulate insulin secretion when the plasma glucose is lower than 60 mg/dL.[30,31] In terms of efficacy, they appear to be similar to metformin, lowering HbA1c levels by approximately 1.5% points.[13]

Chlorpropamide

Chlorpropamide has been available for more than 30 years and is a highly effective OHA with a very long duration of action. The main side effect for type 2 nonpregnant patients is a significantly high rate of severe and protracted hypoglycemia. This complication was not a major concern for pregnant patients in previous studies.[32–43] The drug stimulates antidiuretic hormone secretion enhancing its effect at the renal tubular level that results in water retention and hyponatremia. Since the development of second-generation sulfonylurea drugs that do not cross the placenta (glyburide) and with its high rate of hypoglycemia, chlorpropamide is not recommended for use in pregnancy.[21]

Glyburide (Glibenclamide)

A second generation of hypoglycemic sulfonylureas has emerged that includes glyburide (also known as glibenclamide, glybenzcyclamide, glipizide, and gliclazide.) These drugs are considerably more potent with a shorter half-life time than the first generation. When administered as a single agent, concentration begins to increase within 30–60 minutes. The peak plasma level of glyburide occurs within 2–4 hours and returns to baseline within about 8 hours. However, low but detectable levels may still be evident at 24 hours. The half-life time is approximately 6–10 hours and metabolites may extend the half-life time.[44]

Food digestion does not affect drug absorption. Metabolism of glyburide occurs in the liver and its metabolites extracted in bile and urine in equal proportions. Ten hours is the approximate elimination time (defined as 5× half-life time). Elimination time of a given drug equates to approximately 97% removal. Glyburide clearance is metabolized by the cytochrome P450 enzymes CYP2C9 and CYP3A. The drug converts to one or more metabolic products eliminated in feces and urine.[45–47]

The pharmacokinetic and pharmacodynamics of glyburide is via augmentation of insulin secretion from β-cells by depolarizing them through binding to ATP-dependent potassium-ATP channels. This causes increased insulin secretion. A secondary effect is through increased tissue (muscle, liver, and adipocytes) sensitivity to insulin. This occurs by fasting state glucose lowering mediated through noninsulin-mediated mechanisms. The action probably occurs as the result of decreased glucose and lipid toxicity.[14,15]

How often or how many times daily do patients need to take medications? As a rule of thumb, the shorter the half-life, the more often the patient needs medication. In general, dosing schedules have an importance well beyond medication pharmacodynamics. Medication requiring multiple daily doses has more compliance issues. A major assumption in dosing strategies is that almost

all medication should be at a relatively smooth steady state. To meet body needs for energy through glucose metabolism, there is a need for a constantly fluctuating amount of effective insulin. Nondiabetic women are able to produce this insulin no matter what and when they eat and achieve and maintain a steady metabolic state. Diabetic patients cannot achieve this physiological steady state. They need the additional drug therapy and lifestyle intervention. Steady state exists when defined plasma concentration (peak, average) is identical following each administration. At five times half-life time, a drug concentration is 97% of steady state values regardless of the dose and interval. The relationship between dose interval and half-life determines the need for a loading dose (shorten the time to reach steady state) and dosing schedule.

Adverse effects of the drug are infrequent; they occur in <4% of patients receiving second-generation agents.[21] However, in approximately 11%–38% of type 2 nonpregnant patients, the main side effect of glyburide is hypoglycemia with symptoms being dose related. The patient most receptive to glyburide therapy is one who has been hyperglycemic for less than five years, is willing to follow a dietary protocol, and is either normal weight or obese. Characteristic features of both type 2 and gestational diabetes are β-cell exhaustion and insulin resistance. Most often, patients of both diabetic types are comparable in obesity, asymptomatic in the early stages of the disease, and have similar prevalence in the same ethnic group. Given the similarity of the phenotypic features of these complications, it is safe to assume that the use of glyburide and other potential oral medications may be beneficial in the prevention of maternal/fetal gestational diabetic complications.

Glimeperide

Glimeperide is a sulfonylurea drug. Both this drug and glyburide displace one another from their respective binding sites. Glimeperide has a 2.5–3-fold faster rate of association and 8–9-fold faster rate of dissociation from the β-cells sulfonylurea receptors (SUR) binding site than glyburide. This results in a more rapid release of insulin and a shorter duration of insulin secretion. Glimeperide significantly increases second-phase insulin secretion, whole body glucose uptake and insulin sensitivity.[11,48,49] Demonstration of increased insulin sensitivity revealed lower fasting plasma insulin and C-peptide levels in patients using this drug compared to glyburide-treated patients with comparable levels of glycemia. Glimeperide use in pregnancy remains untested.[11,48,49]

Glinides

Like the sulfonylureas, the glinides stimulate insulin secretion although they bind to a different site within the sulfonylurea receptor. They have a shorter circulating half-life than the sulfonylureas and must be administered more frequently. Of the two glinides currently available in the United States, repaglinide is almost as effective as metformin or the sulfonylureas, decreasing HbA1c levels by about 1.5% points. Nateglinide is somewhat less effective in lowering HbA1c than repaglinide when used as monotherapy or in combination therapy.[50] The risk of weight gain is similar to that of the sulfonylureas, but hypoglycemia may be less frequent, at least with nateglinide, than with some sulfonylureas.[51,52]

Biguanides

Recognition of the biguanide group of drugs came as early as 1920, but received clinical recognition in the United States only in the past two decades. Phenformin, the primary drug in this group, was withdrawn from the United States and European markets because it caused lactic acidosis. Its replacement, metformin, is used extensively in Europe and the United States.[21] In most areas of the world, metformin is the only biguanide available.

Metformin is a second-generation biguanide that has universally been shown to be effective in improving the glycemic profile in diabetic patients. Its major effect is to decrease hepatic glucose output and lower fasting glycemia. Typically, metformin monotherapy will lower HbA1c levels by approximately 1.5% points.[53,54] A multicenter, randomized clinical trial (TODAY study) compared three treatment approaches: metformin monotherapy, metformin and rosiglitazone, and metformin and lifestyle intervention. The study showed a 50% failure rate with metformin alone over an average follow-up of 3.86 years. The combination of metformin and rosiglitazone was superior to metformin alone in sustaining durable glycemic control, and metformin plus lifestyle intervention produced intermediate results.

Similar to adults, the pathophysiology of type 2 diabetes in youth involves peripheral and hepatic insulin resistance, together with impaired β-cell function, which progressively worsens over time. The deterioration in β-cell function in youth appears to be accelerated compared with that observed in adults. Cross-sectional observations, including the TODAY study, showed an inverse relationship between HbA1c and β-cell function and not insulin sensitivity, suggesting that residual β-cell function relative to insulin sensitivity is a determinant of glycemic control in youth with type 2 diabetes.[55]

The mechanism of action in metformin includes decreasing hepatic glucose production and intestinal absorption of glucose and increasing peripheral uptake of glucose and utilization. It results in enhanced insulin sensitivity, that is, decreased insulin requirements. Importantly, metformin does not stimulate insulin secretion, and, therefore, does not cause hypoglycemia either in diabetic or control patients. The drug acts by causing the translocation of glucose transporters from the miscrosomal fraction to the plasma membrane of hepatic and muscle cells.[56] Approximately 50% of the drug is absorbed, with dose-related bioavailability resulting in three hours for immediate and seven hours for extended release. There are differing transporters for gut transport, hepatic accumulation, renal excretion, and slow accumulation into RBCs and into the liver. Pharmacodynamics is delayed, making relevance of short-term pharmacokinetics uncertain. The peak plasma level given as a single agent occurs within four hours. Food intake reduces the extent of absorption although it is administered with meals to minimize gastrointestinal intolerance. In addition, metformin is effective in reducing plasma triglyceride and cholesterol levels as well as promoting weight loss in obese diabetic patients. The half-life time of metformin is about 5–8 hours (in men); however, the concentration-effect relation is uncertain. Metformin is not metabolized; it is excreted unchanged via renal filtration and organic cation transporter–mediated tubular secretion. The elimination of plasma half-life time is approximately six hours. The drug is not metabolized and is eliminated unchanged in the urine. Therefore, patients with renal compromise

should not receive it since the risk of lactic acidosis increases with the degree of renal impairment and patient age. However, recent studies have suggested that metformin is safe unless the estimated glomerular filtration rate falls to <30 mL/min).[57]

Metformin does not stimulate the fetal pancreas to oversecrete insulin. The efficacy of the drug to reverse known defects responsible for insulin resistance in type 2 diabetes and its safety with regard to hypoglycemia suggests that it may be an ideal drug for primary and secondary prevention of gestational diabetes. What we still do not know are the gastrointestinal transit changes in pregnancy that allow us to use extended release metformin rationally. Data on benefit versus immediate release is likely to be limited, at best. Slow accumulation in "effect compartment" limits extrapolation of pharmacokinetic data, alone, to dictating time course of dose titration.

Metformin has no significant effects on the secretion of glucagons, cortisol, growth hormone, or somatostatin. The mechanism by which metformin reduces hepatic glucose production is controversial, but the preponderance of data indicates an effect on reducing gluconeogenesis.[56] It has a strong safety and efficacy record with a frequency of lactic acidosis one-tenth that of the parent drug. The incidence of lactic acidosis with metformin is approximately 0.03 cases/1000 patients annually. Metformin is gradually introduced in 500 or 850 mg increments to a maximum of 2000 mg daily. It is generally well tolerated, with the most common adverse effects being gastrointestinal.[58] Metformin interferes with vitamin B_{12} absorption but is very rarely associated with anemia. The major nonglycemic effect of metformin is either weight stability or modest weight loss, in contrast with many of the other blood glucose-lowering medications. The UKPDS demonstrated a beneficial effect of metformin therapy on CVD outcomes.[27]

TZDs or glitazones are peroxisome proliferator–activated receptor γ-modulators; they increase the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin ("insulin sensitizers").[59] The data regarding the blood glucose-lowering effectiveness of TZDs when used as monotherapy demonstrated a 0.5%–1.4% point decrease in HbA1c. The TZDs appear to have a more durable effect on glycemic control, particularly compared with sulfonylureas.[25] Troglitazone was introduced in 1997 but because of its high rate of hepatic toxicity was withdrawn from the market in 2000. Newer agents in this class such as rosiglitazone and pioglitazone have been widely used in clinical practice without reported hepatic toxicity. However, the September 2003 Mayo Clinic Proceedings reported that both these drugs can cause or exacerbate heart failure and pulmonary edema and should be avoided in patients with left ventricular dysfunction or chronic renal insufficiency. There is need for further studies to understand the mechanism by which these drugs cause fluid overload and deterioration in cardiac status. Since heart failure in pregnant women is uncommon, these drugs may provide still another pharmacological alternative to insulin therapy, although to date, there is no reported data on its use in pregnancy.

These OHAs exert their principal effects by lowering insulin resistance in peripheral tissue. A decrease in systemic and local tissue lipid availability may also contribute to its positive effects in controlling the diabetes. Rosiglitazone and Pioglitazone are absorbed within about two hours, but the maximum clinical effect occurs within 6–12 weeks. It is recommended that liver function be measured before start of therapy and monitored once initiated. Studies also report considerable weight gain with the drugs.[60,61]

The most common adverse effects with TZDs are weight gain and fluid retention, with peripheral edema and a twofold increased risk for congestive heart failure.[62,63] There is an increase in adiposity, largely subcutaneous, with some reduction in visceral fat shown in some studies. The TZDs either have a beneficial (pioglitazone) or neutral (rosiglitazone) effect on atherogenic lipid profiles.[64,65] Several meta-analyses have suggested a 30%–40% relative increase in risk for myocardial infarction with rosiglitazone.[66–68] The care provider needs to use caution in using either TZD on the basis that they are both associated with increased risks of fluid retention and congestive heart failure and an increased incidence of fractures in women and perhaps in men.[69] On the other hand, the Prospective Pioglitazone Clinical Trial in macrovascular events (PRO active) demonstrated no significant effects of pioglitazone compared with placebo on the primary CVD outcome (a composite of all-cause mortality, nonfatal and silent myocardial infarction, stroke, major leg amputation, acute coronary syndrome, coronary artery bypass graft or percutaneous coronary intervention, and leg revascularization) after three years of follow-up. Pioglitazone was associated with a 16% reduction in death, myocardial infarction, and stroke—a controversial secondary end point reported to have marginal statistical significance.[70] In addition, as compared with placebo, pioglitazone reduced the risk of conversion of impaired glucose tolerance (IGT) to type 2 diabetes by 72% but was associated with significant weight gain and edema.[71] Finally, meta-analyses have supported a possible beneficial effect of pioglitazone on CVD risk.[72] There is a direct relation between β-cell rest and β-cell protection. The Tripod and Pipod studies[73,74] reported preservation of the β-cell function and delay or prevention of type 2 diabetes. Protection from diabetes required an increase in insulin sensitivity and is the greatest in women who had the largest reduction in insulin requirements ("B-cell rest"). In the TRIPOD study troglitazone was associated with improvement in insulin secretion after the "wash-out" period in previous GDM patients. Troglitazone reduced the incidence of diabetes by 55% in high-risk Hispanic women. The drug reduced secretory demands placed on β-cells by chronic insulin resistance. Pioglitazone stopped decline of β-cell function that occurred in the placebo group resulting in risk for diabetes of 4.6% during a three-year treatment period. Insulin deficiency is a progressive condition that is not adversely affected if a patient receives sulfonylurea, metformin, or insulin. The effect of metformin, acrabose, and glitazone begins to disappear shortly after the drug is discontinued. When drug use is discontinued, patients remain within the target level of glucose control 1–2 weeks before the "WASH-OUT" effect sets in. Women who were protected during the trial remained protected eight months later and had stable β-cell function over a 54-month period (TRIPOD Study). Currently, in the United States, the TZDs are approved for use in combination with metformin, sulfonylureas, glinides, and insulin.

α-Glucosidase inhibitors

α-Glucosidase inhibitors are less effective in lowering glycemia than metformin or the sulfonylureas, reducing HbA1c levels by 0.5%–0.8% points. Acarbose reduces the rate of digestion of polysaccharides in the proximal small intestine, primarily lowering

postprandial glucose levels without causing hypoglycemia.[21] There is a decrease in the postprandial rise in both normal and diabetic patients. Gastrointestinal side effects require gradual dosage increments over time after initiation of therapy. Malabsorption and weight loss do not occur; however, increased delivery of carbohydrate to the colon commonly results in increased gas production and gastrointestinal symptoms. In clinical trials, 25%–45% of participants have discontinued α-glucosidase inhibitor use as a result of this side effect. This group of drugs can be used as a monotherapy in elderly patients. Typically, they are prescribed in combination with other oral antidiabetic agents and/or insulin.[75,76] However, experience during pregnancy is limited but the few studies demonstrated that glyburide controlled glucose levels more efficiently than acarbose.[77]

Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1) are naturally occurring peptides produced by the L-cells of the small intestine that potentiates glucose-stimulated insulin secretion. In addition, they cause decreased glucagon secretion, inhibit gastric emptying and increase insulin sensitivity in some peripheral tissues. In people with normal glucose tolerance, incretin gut hormones such as GLP-1 account for approximately two-thirds of mealtime insulin secretion. However, this "incretin effect" is severely diminished in people with type 2 diabetes, partially because of reductions in GLP-1 secretion.[78,79] Exendin-4 has homology with the human GLP-1 sequence but has a longer circulating half-life. It binds avidly to the GLP-1 receptor on the pancreatic β-cell and augments glucose-mediated insulin secretion.[80,81] Two GDL-1 receptor agonists are approved: Byetta (exenatide), which is injected twice daily, and Victoza (liraglutide), which is injected once daily. Byetta decreases HbA1c by 0.5%–1.00% and Victoza reduces HbA1c from 0.5% to 1.6%. They both induce weight loss of 2–3 kg and are minimally associated with hypoglycemia. Synthetic exendin-4 (exenatide) was approved in the United States in 2005 for use with sulfonylurea, metformin, and/or a TZD. It is recommended by the American Diabetes Association and the European Association for the Study of Diabetes as a validated second-line therapy.

Amylin Agonists (Pramlintide)

Pramlintide is a synthetic analogue of the β-cell hormone amylin. It is administered subcutaneously before meals and slows gastric emptying, inhibits glucagon production in a glucose-dependent fashion and predominantly decreases postprandial glucose excursions. The major clinical side effects are gastrointestinal in nature. Approximately 30% of treated participants in the clinical trials developed nausea, as with exenatide. Some of the weight loss may be the result of gastrointestinal side effects. Currently, pramlintide is approved for use in the United States only as an adjunctive therapy with regular insulin or rapid-acting insulin analogues.

Dipeptidyl Peptidase-4 Inhibitors

GLP-1 and glucose-dependent insulinotropic peptide (GIP), the main insulinotropic peptides of intestinal origin (incretins), are rapidly degraded by dipeptidyl peptidase-4 (DPP-4). DPP-4 is a member of a family of cell membrane proteins that are expressed in many tissues, including immune cells. DPP-4 inhibitors are small molecules that enhance the effects of GLP-1 and GIP, increasing glucose-mediated insulin secretion and suppressing glucagon secretion. The first oral DPP-4 inhibitor, sitagliptin, was approved by the Food and Drug Administration in October 2006 for use as a monotherapy or in combination with metformin or TZDs. They do not cause hypoglycemia when used as monotherapy. A fixed-dose combination pill with metformin is available. The potential for this class of compounds to interfere with immune function is of concern; an increase in upper respiratory infections has been reported.[78,79,82,83]

The reader should consider the following "drug compass" when contemplating the use of an oral antidiabetic medication in pregnancy:

1. Will the drug–drug interactions complicate its use with the necessary and commonly administered drugs?
2. Can targeted glycemic levels be achieved by using the optimal dose?
3. After nutrient ingestion, can the drug reduce the time lag between plasma glucose rise and insulin secretion?
4. Can serious postprandial and fasting hypoglycemic episodes be minimized because of the short drug duration of action?
5. Are there any side effects that can reduce the long-term beneficial effects?

In summary, the use of an oral antidiabetic drug should provide safety from any toxic effect of drug usage. However, even after addressing this demand, an equally important requirement is the drug's ability to achieve the level of glycemic control targeted in pregnancy. In general, the targeted level of glycemic control is much lower than that recommended in the nonpregnant state. Furthermore, as type 2 diabetes progresses, the ability of β-cells to respond to monotherapy is reduced. In fact, in the majority of type 2 patients, monotherapy failed to achieve HbA1c < 7%. In the UKPDS, this was true for both glyburide and metformin-treated patients. Approximately 50% of patients needed more than one oral antidiabetic agent to obtain targeted levels of glycemic control. Therefore, the use of antidiabetic drugs as an effective therapy in type 2 pregnant women is questionable. In contrast, gestational diabetes, which is a milder form of glucose tolerance, will most likely respond to this therapy (Figure 27-2).

The Rationale for the Use of Antidiabetic Agents in the Management of GDM

The underlying principle for the use of antidiabetic agents is motivated by three factors:

1. Similarity between type 2 diabetes and GDM. In addition to the insulin secretion and resistance abnormalities found in both conditions, there is a loss of first-phase insulin secretion with a striking lag time between the postprandial rise in glucose and the presence of significant insulin at the peripheral sites.[28,31] This will result in an early increase in postprandial glucose values. As discussed before, second-generation sulfonylurea agents are rapid in onset and have short duration of action that make them ideal agents to treat very early stages of type 2 and possibly GDM patients.
2. GDM and patients with IGT are characterized by a mild hyperglycemia in comparison to type 2 diabetic women. However,

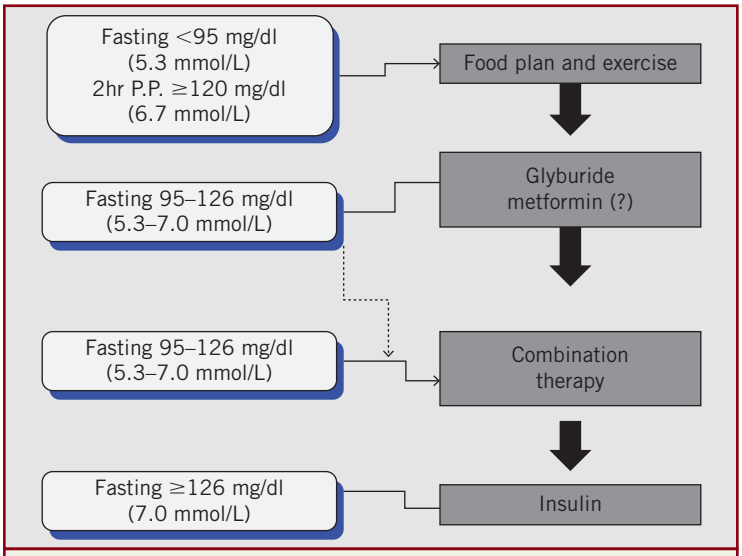

Figure 27-2 Steps in GDM management: Decision path.

this mild hyperglycemia is significantly elevated in comparison to nondiabetic women. As the disease progresses to type 2 diabetes, there is progressive loss of β-cell function.[11,84,85] In the presence of insulin resistance with obese, pregnant, and especially GDM women, insulin secretion will initially increase to compensate for the impairment in insulin action. The ensuing decrease in secretion over time will, in turn, result in the progression from normal glucose tolerance to gestational diabetes; from there to IGT to type 2 diabetes.[11,85] OHAs have successfully been used to decrease glycemic levels in type 2 diabetes. Since GDM subjects have the mildest form of the glucose tolerance abnormality, it is reasonable to assume that the use of oral antidiabetic agents in the treatment of GDM should be even more effective than its current use with type 2 diabetes.

3. The UKPDS of type 2 diabetes supported the efficacy of these drugs and in particular the use of glyburide. The study demonstrated that with the use of glyburide, 70% of the patients achieved a targeted level of glucose control with the most favorable effect achieved within the first five years of therapy. The study also reported a decrease in microvascular and macrovascular complications. Rather than credit a specific therapy as the factor responsible for reduced risk of complications, the authors concluded that improvement in glycemic control was the crucial factor in treating the disease.

The UKPDS and Diabetes Control and Complication Trial[86] studies suggest that intensive therapy in patients with types 1 and 2 diabetes will result in improved glycemic control and decrease in complication rates. Thus, intensified therapy can provide the primary prevention for diabetic complications. Studies of pregnant diabetic women including the study of over 2000 gestational diabetic women[1] demonstrated that intensified therapy will result in improvement in glycemic control and perinatal outcome similar to that in nondiabetic women.

Since gestational diabetes is characterized by a milder glycemic profile and occurs 2–10 years earlier than type 2 diabetes, the use of OHAs to treat GDM patients should prove to be even more efficacious. In addition, it is reasonable to expect that the success rate for the therapy with GDM patients should be at least within the 70% rate or higher that was achieved with type 2 diabetics. In evaluating the use of glyburide in comparison to insulin[20] we found that glyburide in GDM patients is as effective as the use of insulin when 82% of the glyburide and 88% of the insulin patients achieved the targeted levels of control. In another randomized study[40] 80% of subjects treated with oral agents or diet maintained targeted blood glucose levels of <150 mg/dL. In contrast, only 38% of the insulin patients were able to achieve this level probably due to poor compliance. The majority of studies reporting treatment with glyburide have shown 70%–85% success rate. However, the success rate is dependent upon the severity of the disease, rate of obesity, and quality of care for a given population.

Two studies examined the level of compliance in women using glyburide therapy. In both studies, the sample sizes were relatively small and the authors reached contradicting conclusions. In the first study of 42 women with GDM, success with glyburide was defined as maintaining fasting plasma <90 mg/dL and one-hour postprandial <130 mg/dL. Approximately 83% of the women achieved these goals with universal satisfaction with the mode of therapy.[87] In the other study, 73 women who had refused insulin therapy were assigned to glyburide. Success of therapy was defined as achieving 80% or more of capillary blood values within normal glycemic levels. Approximately 47% of the subjects failed to achieve the targeted glycemic goals after 1–9 weeks of treatment.[88]

Analysis of this study revealed several confounding design flaws. The authors used a nontraditional method of glyburide administration. The initial dose was too large, the increments too rapid (in some cases every three days) and the maximal dose too small (17.5 mg). Finally, the duration of glyburide treatment was too short (1–9 weeks). The above factors suggest that a large number of patients did not receive a sufficient glyburide dose and/or

insufficient time had elapsed for subjects to achieve targeted goals. It is interesting to note, however, that none of the newborns demonstrated signs of hypoglycemia after delivery.[88]

Success in achieving targeted levels of glycemia will vary from study to study because of different doses, administration algorithm, length of therapy, type of patient (severity and ethnicity), and comparable groups (compliant vs. noncompliant subjects). Finally, to date, there is no evidence that a diabetic medication will be able to maintain targeted levels of glycemic control in all patients. For example, in our study[20] only 88% of the insulin-treated patients achieved targeted levels of control. As a rule of thumb, the physician must always consider the efficacy of his treatment rather than censuring the drug for failure to achieve targeted levels of glycemic control and desired pregnancy outcome.

WHAT TO CONSIDER WHEN YOU CONSIDER DRUG DOSAGE?

Empiric dosing and titration based on nonpregnant pharmacokinetic (PK) alone is not defensible. Given the approximate doubling in glyburide clearance during pregnancy, should we increase the starting and maximal dose during pregnancy? Should dosage interval be shortened (due to short half-life time)? Given the extraordinarily short half-life time of glyburide and other medications in pregnancy, why would the clinician wait more than 1–2 days for dose titration? Does timing of dose versus food intake matter? Based on PK-PD (pharmacodynamic), should combination therapy be a consideration (metformin, glyburide, pioglitazone)? None of these questions have been adequately addressed and, therefore, there is paucity of conclusive data. From the scientific perspective, it is important to understand the pharmacokinetic and pharmacodynamic considerations. However, in the clinical, real world environment, drug management decisions need to be determined based on patient's diet, weight, and ethnicity. For example, the glycemic benefits of sulfonylureas are nearly fully realized at half-maximal dose, and higher doses should generally be avoided. In our study, 31% of GDM subjects achieved targeted levels of glycemic control with a 2.5 mg dose. Twenty-seven percent required 5 mg; 21%–10 mg, 9%–15 mg, and only 12% required the maximal dose of 20 mg.[89]

Thus, approximately two-thirds of the patients achieved targeted levels of glycemic control with <50% of the maximal dose. In light of this clinical data, combination therapy with lower doses of each medication should be considered to successfully maximize glucose control. The upper therapeutic range in which no more than 5%–10% of patients will experience unacceptable toxic effect is a major consideration. The goal is to provide drug efficacy without unacceptable toxicity.[90] Combination therapy with insulin plus oral agents may provide an advantage since it will result in a lower dose for each drug.[91]

Algorithms for glyburide administration that consider the above factors are shown in Figures 27-2 and 27-3.

Animal Studies and Oral Agents

The incidence of congenital anomalies in nondiabetic women is 2%–5%. This rate increases to 7%–9% overall in pregnant diabetics and will be even higher in poorly controlled diabetes and as the severity of the disease increases. Unanswered questions remain: What is the toxic agent that triggers the development of malformations? Is it the glucose or is it the oral antidiabetic agent? This dilemma has led to several investigations in animal species or tissue cultures as a source for the answers. These types of studies provide the conditions with which to test separately and together the effect of different drug doses in conjunction with varying levels of glucose. However, a major difference exists between laboratory mice and the human embryo.

Smithberg[92] studied different hypoglycemia-inducing treatments that included insulin and tolbutamide in fasting of prepuberal mice, as well as combination treatments involving nicotinamide plus insulin or tolbutamide. The drugs were potent teratogens in one or more inbred strains of mice. Teratogenic treatments, with the exception of fasting, also caused a variable proportion of deaths. The response of different strains of mice to individual treatments relevant to teratogenicity or lethality was highly variable. The most pertinent finding in these experiments was the response variability elicited from each strain of mouse, that is, the 3% mortality following insulin treatment in strain BALB/c as compared to 17% in strain 129. This example demonstrates the variability in study results reported in the literature. It is also noteworthy that the mice strain was the determining factor to recommend or fail

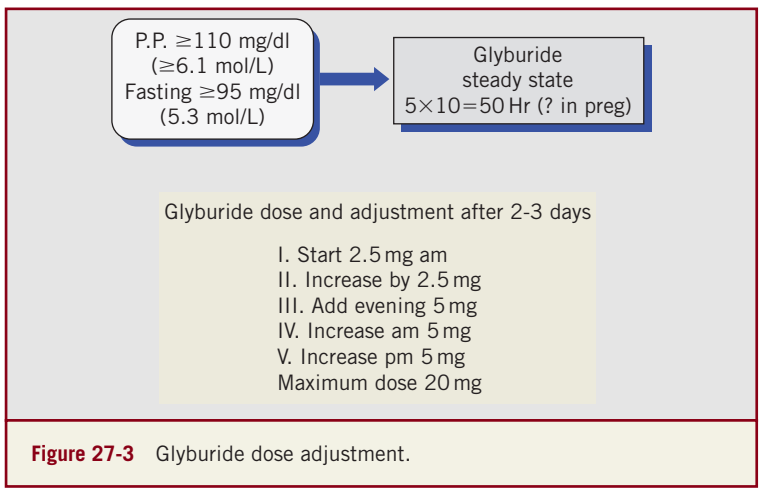

Figure 27-3 Glyburide dose adjustment.

to recommend a particular drug. First-generation sulfonylureas, such as tolbutamide and chlorpropamide in the majority of animal studies are associated with congenital malformations. Adverse effects appear to be caused by the drugs and not by the hypoglycemia they produce. Chlorpropamide appeared to be embryotoxic in mouse embryos in culture.[93–95] To date, no animal studies have evaluated second- and third-generation sulfonylureas and their association to malformation.

Denno and Sadler[96] evaluated the effect of biguanides: metformin and phenformin as embryotoxic agents at concentrations equal to serum levels obtained in patients treated with the agent clinically. They found that phenformin is embryotoxic, whereas metformin is not, suggesting that metformin is also the safer drug during pregnancy in patients with type 2 diabetes. However, in this study, metformin was not without adverse effects since it produced a delay in neural tube closure and reduced yolk sac protein values at two different concentrations. Although delayed closure of the neural tube may not have resulted in gross morphological abnormalities, it was not possible to assess subtler alternations that might result from such a delay using the culture system.

Shepard[97] and Schardein[98] reported that metformin did not appear to be a major teratogen because <0.5% of the rat fetuses in mothers administered 500–1000 mg/kg developed anophthalmia and anencephaly. However, evidence of embryotoxicity was evident with higher doses of the drug. Since animal studies are not conclusive about the safety of the human fetus regarding the association between drugs and malformations, additional research approaches are needed to determine drug transfer across the placenta and/or tests of fetal blood for evidence of the drug.

WHICH ANTIDIABETIC DRUGS CROSS THE PLACENTA AND IF THEY CROSS, WHAT ARE THE EFFECTS ON THE FETUS?

A major consideration in the efficacy of the drug will be its ability to cross the placenta. If it crosses the placenta, what toxicity, if at all, can it cause the developing fetus? Often, the fear of drug-induced adverse outcome, especially after the thalidomide era in the 1960s, paralyzes the physician's ability to judge the scientific rationale for using a drug and evaluating it using evidence-based data instead of dogma. Very few medications have been shown *not* to cross the placental barrier. In fact, a pregnant woman is often exposed to four to five prescription drugs during the pregnancy for a variety of complaints. Similar to other epithelial barriers, transfer of drugs across the placenta is affected by several factors: molecular weight; p*K*a; lipophilicity; placental blood flow; blood protein binding; elimination half-life; and, the specific placental transport system that affects the ability of drugs to enter the fetal compartment (e.g., extruding drug pumps such as P-glycoprotein).[90,99,100]

Unlike other species, the human placental barrier is composed of a single rate-limiting layer of multinucleated cells, the syncytiotrophoblasts. During the formation of the placenta, fetal tissues erode the maternal blood vessels to attain a closer proximity to the maternal circulation. Chorionic villi that contain fetal blood vessels infiltrate the maternal vessels and establish a sinusoid in which the villi are suffused by maternal blood.[99–102] The rate-limiting barrier for penetration across the human placenta is the syncytiotrophoblast layer. Therefore, animal studies addressing placental transfer (e.g., mice) will not be necessarily applicable in humans.[103] A typical question raised is if the placenta during the first trimester has the same characteristics of those from the late second and third trimesters upon which the majority of studies were performed. Although there is paucity of information, it has been suggested that there is no difference in placental transfer in different trimesters.[104] Although the cutoff for actual molecular weight passage across the placental barrier has not been accurately defined, it is generally agreed that molecular weight of ≤1000 Da passively permeates across the placental barrier with sustained maternal blood concentrations (Table 27-2).[105,106]

The recirculating single-cotyledon human placental model is widely used to characterize the transport and metabolism of numerous drugs and nutrients. It is a reliable in vitro model for human placental transfer since it facilitates the study of intact human placenta independent of fetal metabolism. Experiments validate against known substances that freely cross the placenta.[104,107,108]

In our studies, we evaluated if first- and second-generation sulfonylureas will cross the placenta.[109–111] Glyburide's molecular weight is 494 units; it is one of the largest oral hypoglycemic or antihyperglycemic agents. We investigated[111] the transport and metabolism of glyburide across the human placenta. We found that (1) there was virtually no significant transport of glyburide in either maternal-to-fetal or fetal-to-maternal directions with an

TABLE 27-2 Characteristics of Selected Oral Antidiabetic Drugs

	Metformin	Acarbose	Glyburide	Rosiglitazone	Pioglitazone
Molecular weight	166	646	494	474	393
Half-life	6.2 h	2 h	10 h	3–4 h	3–7
p*K*a	12.4	5.1	5.3	6.8	NA
Lipid solubility	Freely in H_2O	Freely in H_2O	Readily soluble	Readily soluble	Readily soluble
Metabolites	Nonactive	In intestine (bacteria)	Nonactive	Nonactive	Nonactive
Protein binding	Minimal	NA	99.8	99.8	99.8
Peak	7 h	1 h	4 h	1 h	2 h

Abbreviation: NA, not yet available.

average transport of 0.26% at two hours. These levels are three- to eightfold higher than the therapeutic peak levels after a 5 mg oral dose in humans. In fact, when we tested cord blood samples using high-performance liquid chromatography (HPLC) technique, glyburide was undetectable in samples despite maternal plasma levels of 50–150 nanograms (ng)/mL. (2) When glyburide concentration was increased 100 times above the therapeutic levels, transport was not appreciably altered. Equilibrium dialysis demonstrated that at least 98% of the glyburide was protein bounded. (3) Glyburide is not captured or metabolized by the placenta.

We also demonstrated[109,110] that second-generation OHAs (especially glyburide), do not significantly cross the diabetic or nondiabetic placenta. Fetal concentrations reached no more than 1%–2% of maternal concentrations. Although glipizide crossed the placenta in small amounts, this was significantly higher than glyburide. In contrast, tolbutamide diffused across the placenta most freely. Glyburide has not been demonstrated to be teratogenic in animal studies, and is thus classified as a Category B agent.

Our clinical study confirmed our basic science studies[109–111] that glyburide does not cross the placenta in significant amounts. Glyburide was undetectable in cord serum to the level of sensitivity of the test. As a quality control, we obtained simultaneous samples of maternal serum from 12 women at the time of delivery to determine whether sufficient gradient levels for glyburide exist. Maternal levels ranged from 50 to 150 ng/mL. To ascertain any potential effect of glyburide on fetal pancreas, we compared insulin umbilical cord levels between the two groups. The mean cord-serum insulin concentrations were similar for both groups.

Mechanism That Prevents Glyburide From Crossing the Placenta

Late pregnancy is characterized by a major increase in glomerular filtration rate, tubular secretion, hepatic blood flow, and protein binding. These physiological factors affect drug interaction. The increase in drug clearance rate is due to the enhanced function of different cytochrome P450 enzymes, and so forth. Therefore, most likely, there will be a need for larger doses to achieve therapeutic steady state concentrations.[112,113] Glyburide has a relatively short elimination half-life time (6–8 hours) and an extremely high protein binding (99.8%) that results in minimal placental transfer. Furthermore, there is effluxing of glyburide by specific placental transporters (e.g., P-gP, MRP1, MRP3, MRP3, and BCRP) even against concentration gradients from the fetal to the maternal side.[114,115]

More significantly, regardless of the mechanism responsible for inhibiting transfer, we demonstrated that neonatal cord insulin was nonsignificant between insulin and glyburide-treated women (15 ± 2.3 microunit [μU] and 14 ± 4 μU, respectively). In addition, maternal C-peptide levels at entry to the program were 2.7 ± 1.5 versus 2.9 ± 1.3 (ng/mL) (nonsignificant). During delivery, C-peptide levels were significantly elevated in glyburide-treated women (3.4 ± 1.1 vs.3.8 ± 1.1).[20] It should be noted that when measuring placental transfer, one needs to understand the limitations of the measurement system and the unit of measure, that is, 1 mg = 1000 microgram (μg); 1 μg = 1000 ng; therefore, 1 mg = 1,000,000 ng. Two measuring systems were used to evaluate placental drug transfer. One is HPLC-ultra violet (UV) and the other LC-MS/MS (liquid chromatography tandem mass spectrometry). Regression analysis comparing glyburide transfer measured in each system revealed a strong association ($y = 0.9321x + 6.9427$, $r^2 = 0.9597$).[116–118]

We,[20] using HPLC/UV, whose limit of detection is 10 ng/mL, found that glyburide was not detected in any sample of umbilical cord. Hebert et al.[119] using LC-MS/MS found umbilical cord venous concentrations ranging from the limits of assay detection, from 0.13 to 0.25 ng/mL to 12.5 ng/mL. Of note, concentration is time dependent; therefore, the lag time from administration to sample collection will influence drug concentration (Cp). In contrast, the ratio is the result of the drug concentration at a given time between two components, fetal and maternal. Therefore, varied lag time affects concentration levels that result in different ratios. In fact, different studies reported varying lag times. Langer et al.[20] reported a lag time of 8 ± 4 hours from last dose to sampling. This resulted in a glyburide concentration of 50–150 ng. Gedeon et al.[114] reported maternal glyburide plasma concentration of 245 ± 109 ng, but no lag time from administration to sampling was given. These examples demonstrate the need for caution in describing methods of measurement and in comparing research studies. Hebert et al.[119] reported "…maternal plasma glyburide with concentrations from less than the limit of assay quantitation to 32.7 ng/mL at delivery with up to 13 hours from administration to sampling." The umbilical venous/maternal glyburide ratio at delivery demonstrated mean umbilical cord/maternal glyburide concentration ratio of 1.0 ± 1.2. When data from the sole outlier was excluded, the mean ratio was 0.7 ± 0.4. In 20% of the umbilical cord collected at delivery, glyburide plasma concentration was greater or equal to the mean maternal steady state concentration. However, when glyburide concentration data was stratified for fetal concentration, four infants had <1 ng/mL; seven infants 1–3 ng/mL; five infants 3–12 ng/mL resulting in mean glyburide concentration of approximately 1 ng/mL.[119] This study is a perfect example of how faulty interpretation of data may lead to erroneous conclusions. The study suggested that over 70% of the maternal glyburide was transferred through the placenta to the fetus. This is in contrast to multiple perfusion studies that indicated conclusively that minimal nonsignificant amounts of glyburide crossed the placenta. This negligible transfer will occur in the majority of perfusion studies regardless of the tested drug. In fact, the study demonstrated a minimal glyburide concentration in the fetal compartment (~ 1 ng/mL), which is most likely of nonclinical significance. This demonstrates the need for caution in distinguishing between ratio and actual concentration levels in measurement.

…AND WHAT ABOUT INSULIN?

Insulin will lower glucose and HbA1c and is also the most effective at lowering glycemia. Insulin can, when used in adequate doses, decrease any level of glycemia to, or close to, therapeutic goals. Insulin therapy has beneficial effects on triacylglycerol and high-density lipoprotein cholesterol levels, especially in patients with poor glycemic control, but is associated with weight gains of about 2–4 kg and risk of hypoglycemia. The higher the dose, the greater the likelihood of adverse effects. Generally, long-acting insulin analogs reduce the incidence of overnight hypoglycemia, and rapid-acting insulin analogs reduce postprandial glucose excursions as compared with corresponding human insulins (neutral protamine hagedorn [NPH], Regular).

When glucotoxicity is resolved and the metabolic state stabilized, it may be possible to taper insulin partially or entirely, especially in type 2 and GDM patients. It may then be efficacious to transfer these patients to noninsulin antihyperglycemic agents or in combination with insulin. Unlike the other blood glucose-lowering medications, there is no maximum dose of insulin beyond which a therapeutic effect will not occur. Relatively large doses of insulin (≥1 unit/kg) are needed.[120] Although initial therapy is aimed at increasing basal insulin supply, usually with intermediate- or long-acting-insulins, patients may also require prandial therapy with short- or rapid-acting insulins. The very rapid-acting and long-acting insulin analogues have not been shown to lower glycemic levels more effectively than the older, rapid-acting, or intermediate-acting formulations.[121–124]

The question remains, does insulin cross the placenta? In the early 1980s, it was demonstrated that beef–pork insulin (antibody) crosses the placenta probably by changing the formation (size) of the antibody insulin complex.[125] A decade later, it was again shown that insulin crosses the placenta and may influence the development of fetal macrosomia.[126] Lindsay et al.[127] in 2004 reported that insulin antibodies were detected in the cord blood of 95% of the offspring at birth. McCance et al.[128] evaluated the presence of insulin antibodies and their effect on placental transfer with insulin aspart. They concluded that insulin antibodies do not develop during pregnancy with the use of aspart in type 1 diabetes. With the use of human insulin, 1%–5% of insulin concentration in the maternal artery will be transferred to the fetal circulation.

Although it was demonstrated that insulin antibodies do not develop during pregnancy with the use of insulin analogs (aspart, lispro, and glargine), it was not clear if insulin analogs cross the placenta. Boskovic et al.[129] studied this topic. They found that no placental transfer could be detected during perfusion with 100 and 200 μU/mL. In contrast, there was a small concentration-dependent transfer to the fetus at concentrations of 580 μU/mL and higher, detectable after at least an hour of constant concentration of insulin lispro during perfusion. Measuring lispro levels in 11 pregnant women revealed that a 50-unit dose may achieve serum concentrations of >200 μU/mL with apparent linear correlation between dose and levels. A dose of ≥580 U/mL is equal to approximately 75 units of insulin. They concluded that insulin lispro is unlikely to cross the placenta at a single standard dose and is also unlikely to reach or harm the unborn baby. Their conclusion was based on the assumption that type 2 and GDM women will never receive this amount of insulin. However, this is an erroneous conclusion since these patients are obese, many morbidly obese, characterized by insulin resistance and require much larger insulin doses.

Holcberg et al.[130] reported that insulin lispro does not cross the placenta in a placental perfusion study. The maternal steady state reached 48 μU in the maternal artery and 28 μU in the maternal vein while in the fetal side insulin lispro was not detected. However, the concentration of insulin lispro in placental tissue was 1836 + 220 μU. Kraemer et al.[131] demonstrated the first direct evidence of active glyburide transport from the fetus to the mother and, in general, of any medicinal drug used during pregnancy. Their results suggest that glyburide is actively effluxed by a transporter other than P-glycoprotein. Alternatively, it is possible that a minority of glyburide is carried by P-glycoprotein, but most of the fetal load is pumped to the mother by a yet-unidentified placental transport system.

Regarding long-acting insulin analogs (glargine), two studies addressed this issue. One concluded that glargine probably does not cross the placenta. Reduced maternal steady state concentrations may suggest insulin uptake by the placenta.[132] In another study by Pollex et al.,[133] insulin glargine at a therapeutic concentration of 150 pmol/L (20 μU/mL) was added to the maternal circulation. Experiments were carried out at insulin glargine concentrations 1000-fold higher than therapeutic levels (150, 225, and 300 mmol/L). Concentrations of 150 pmol/L of glargine showed no detectable insulin levels in the fetal circulation. After perfusion with concentrations of 150, 225, and 300 nmol/L, the rate of transfer remained low at 0.079 ± 0.01, 0.14, and 0.064 pmol. min(–1). g tissue(–1), respectively. This demonstrates that transfer begins when the glargine dose is >0.3 unit/kg. They concluded that insulin glargine, when used at the therapeutic concentrations is not likely to cross the placenta. Again, the conclusions are flawed because they are based on the assumption that their designated therapeutic level is universal. We acknowledge that therapeutic levels will be different in different centers related to policy, rate of patients that achieve targeted glycemic goals, obesity, and so forth.

Metformin, another oral agent that is commonly used, transfers readily from the maternal to fetal circuit across placentas that were obtained from uncomplicated pregnancies and pregnancies with gestational diabetes.[134,135] Since metformin is a polar positively charged compound, an effort was made to characterize its permeability across the human placenta using the ex vivo placental perfusion model. It was found that metformin permeability across the placenta is mediated by a carrier that transports cationic compounds bidirectionally with a higher transfer rate from the fetal to the maternal side.[136]

Rosiglitazone has been classified in pregnancy as a C drug. No ill effects on implantation teratogenicity have been observed in animal studies using 20–75 times the maximum recommended human daily dose. However, use of rosiglitazone in rat and rabbit models during the mid-gestation to late gestation have been associated with fetal growth restriction and death after exposure to doses exceeding four times the maximum recommended human daily dose. Similarly, fetal effects have not been observed at doses less than four times the maximum dose. Placental transfer of the drug in the ex vivo human perfusion model found that there is minimal transfer and fetal accumulation.[137] Nanovskaya et al.[138] showed that the binding of glyburide and rosiglitazone to albumin is similar but it is only one of the factors that could affect their placental transfer and distribution. In another study, Chan et al.[139] evaluated rosiglitazone concentration in fetal tissue and coelomic and amniotic fluids in 31 women undergoing surgical termination of pregnancy at 8–12 weeks' gestation. They concluded that the risk of placental transfer of rosiglitazone is much higher at or after 10 weeks' gestation. Absence of detectable rosiglitazone in amniotic fluid despite its presence in fetal tissue suggests that fetuses may have the ability to metabolize the drug and scant parent drug was excreted unchanged in urine.[139] In summary, the current accepted understanding is that most drugs administered during pregnancy can permeate the placental barrier. There is sufficient evidence to suggest that the placenta is capable of limiting fetal exposure to the drug especially in the case of glyburide. What is important for all drugs, from oral to insulin, is not which

crosses the placenta and in which quantities but rather which one may adversely affect the fetus. To date, thousands of patients have been treated with glyburide, metformin, and insulin during pregnancy with no teratogenic effect on the baby. Patients should not be denied the better treatment option and benefits provided by these drugs; at the same time, future investigations should continue to determine their safety just as they would for any other drug in pregnancy.

CLINICAL STUDIES

Does Hypoglycemia and the Rate of Fetal Anomalies Increase With Glyburide and/or Metformin Therapy?

Despite the proliferation of information on the efficacy of the use of antidiabetic agents in pregnancy (mainly glyburide and to a lesser extent metformin), their role is not yet universally accepted in the management of GDM. For years these drugs have been prescribed in Europe and South Africa without or minimally reported adverse side effects to the fetus.[32–43] The historic ban in the United States on the use of OHAs in pregnancy has been based on scant evidence of case reports[140,141] and one study in particular on fetal anomalies in 50 poorly controlled type 2 diabetic women before pregnancy[142] *begging the question: Is it the drug or is the glucose?*

The recommendation for the injunction stems from the potential adverse effect on the developing fetus with the assumption that significant transfer occurs across the placenta. Three issues of concern include (1) increased rate of congenital anomalies, (2) the possible induction of fetal macrosomia due to direct stimulation of the fetal pancreas resulting in hyperinsulinemia, and (3) the increased rate of hypoglycemia due to fetal hyperinsulinemia. The source for the above concerns is from case reports or small retrospective studies, the majority of which were published in the 1960s and 1970s. The patient populations were mainly type 2 diabetics. The drugs used in these studies were mainly first-generation sulfonylureas.[140–142]

An example of a study used to generate the recommendation that there is an increased risk for neonatal hypoglycemia with the use of these drugs was a case report of three infants whose mothers received chlorpropamide and another mother of an infant given acetohexamide; another case report reported prolonged symptomatic neonatal hypoglycemia.[140,141] Maternal hypoglycemia is a known side effect of sulfonylureas. We evaluated the rate of maternal hypoglycemia in several studies. In a randomized study, we found a significantly higher hypoglycemia rate (12% vs. 20%) for the insulin-treated patients.[20] In another study, using continuous blood glucose, we evaluated the rate of hypoglycemia that was defined as <50 mg/dL. In insulin-treated patients the rate was 63% with a mean of 4 ± 1 episode /d. The rate of glyburide-treated patients was 28% with a mean of 3 ± 1 episode/d.[143] In an additional study of 675 subjects, with mean blood glucose determinations of 310 ± 190 for each subject, 90% of the patients had no episodes of hypoglycemia for episodes defined as <40 mg dL. Sixty-five percent of subjects had no episodes of hypoglycemia defined as 40–50 mg/dL. One to four episodes of hypoglycemia were reported in <10% of subjects. A significant association was found between the incidences of maternal asymptomatic hypoglycemia and mean blood glucose. No association was found between glyburide dose and the rate of maternal asymptomatic hypoglycemia. No association was shown between glyburide dose and/or mean blood glucose and the incidence of neonatal hypoglycemia.[144] Regarding neonatal hypoglycemia, two meta-analyses demonstrated that there was no difference between insulin and glyburide neonates.[145,146] In relation to level of glycemia during pregnancy, the rate of neonatal hypoglycemia was similar in well and poorly controlled mothers and not dose related.[144] The maternal rates of hypoglycemia in glyburide-treated patients may be explained by the extensive insulin resistance due to pregnancy, which serves as a protective mechanism. The similar rates of hypoglycemia in neonates of mothers treated with glyburide or insulin is explained by the negligible amount of glyburide that crosses the placenta.

The recommendation not to use oral hypoglycemic or antihyperglycemic agents because of increased rate of anomalies was based on a retrospective study involving 20 type 2 patients all with hyperglycemia before conception (HbA1c > 8%).[142] The fact that maternal hyperglycemia existed preconception makes it impossible to determine if the increased rate of anomalies found in these study subjects was a result of the medication or the elevated glucose level. In contrast, several studies in the past decade suggest that there was no association between OHAs and congenital malformations.

Towner et al.[147] treated 332 type 2 patients with OHAs or insulin before pregnancy. The authors demonstrated that mode of therapy did not have an adverse significant effect while level of glycemia and maternal age was significant factors contributing to the rate of anomalies. We found similar findings[148] in type 2 diabetic women exposed to different OHAs, insulin, and diet therapy before and during the first trimester of pregnancy. Again, it was the blood glucose and not the mode of therapy that had the net effect on the rate of anomalies. Finally, Gutzin et al.[149] evaluated the safety of OHAs in the first trimester using meta-analysis of 10 studies. They demonstrated that the use of oral antidiabetic agents have no effect on the rate of fetal anomalies, confirming previous basic science studies. In another meta-analysis (eight studies), metformin treatment was associated with 57% protective effect (control 7.2% vs. 1.7% metformin-treated). There was no evidence for increased risk for major malformations.[150] In another meta-analysis, the authors concluded that metformin is comparable to insulin in glycemic control and neonatal outcomes. It might be more suitable for women with mild GDM. This meta-analysis also provided some significant benefits and risks of the use of metformin in GDM and helped to inform further development of management guidelines.[151]

To date, no randomized clinical study has addressed the use of OHAs during organogenesis. The results of the early small-scale studies suggest that an association exists. However, these studies did not control for level of glycemia. The above large-scale studies, although retrospective, as well as the meta-analyses demonstrated that the cause of anomalies is level of glycemia and not the use of oral hypoglycemic drugs. It remains unresolved if the treatment of type 2 diabetes with OHAs will accelerate the rate of anomalies. On the other hand, are we over reacting by condemning these medications? With existing data, care providers need to present information to patients so that issues are addressed and informed decisions made. Moreover, we should be diligent in separating data from type 2 diabetes when speaking about GDM.

In the case of GDM, the issue of anomalies is simpler. GDM patients are diagnosed and enter therapy after the first trimester (after organogenesis period). Then, the concerns remain about potential fetal hypoglycemia and stimulation for macrosomia if the drug crosses the placenta. However, as previously discussed, glyburide does not cross the placenta and therefore cannot stimulate adverse effects in the fetus. Finally, our study[20] provides clinical support for this concern. We demonstrated that in patients who entered therapy after the first trimester, the rate of anomalies was comparable for insulin and glyburide-treated patients and similar to the rate reported in the nondiabetic general population. In summary, GDM occurs in the majority of cases after the first trimester, which is after organogenesis (first 5–7 weeks of pregnancy). Thus, the fetus of the GDM mother is at no risk for congenital malformation. The drug does not transfer across the placenta and demonstrates comparable efficacy to insulin in treating GDM. All these factors make it a potentially attractive drug alternative for management of GDM patients.[20]

What Are the Most Effective Treatment Modalities for Women with GDM?

Several retrospective[36–39,41,42,87,152–161] and 12 randomized studies evaluated the use of sulfonylurea drugs (first and second generations) and metformin during pregnancy.[20,40,162–171] The bulk of retrospective studies concluded that glyburide was as effective as insulin in achieving glycemic control with similar perinatal outcomes (Table 27-3). The randomized studies (Table 27-4) demonstrated that glyburide can effectively provide the medication when diet fails. This conclusion was reiterated by meta-analyses[145,146] (Table 27-5).

In 1971, Notelowitz et al.[38,40] studied the efficacy of first-generation sulfonylureas (tolbutamide, chlorpropamine), diet, and insulin in a randomized study design. The study contained a small sample size with relatively low power when each of the four arms contained approximately 50 patients. No significant difference for perinatal mortality and congenital anomalies was found. Good control was defined as blood glucose <150 mg/dL. Eighty percent of the patients using OHAs or diet and 36% of the insulin-treated patients achieved the targeted level (<150 mg/dL).

Our randomized clinical trial of 404 women compared glyburide- and insulin-treated patients.[20] The blood glucose profile before initiation of therapy was comparable for both groups (114 ± 9 mg/dL vs. 116 ± 22 mg/dL, respectively). Patients were randomly assigned to receive either glyburide (n = 201; initial dose 2.5 mg orally, increasing by 5 mg/wk up to a total of 20 mg) or insulin (n = 203; initial dose 0.7 U/kg subcutaneously three times/daily, increasing each week as necessary) for glycemic control. Patients were required to measure glucose values seven/daily. The target for glycemic control was mean blood glucose levels of 90–105 mg/dL, a fasting blood glucose level of 60–90 mg/dL, a preprandial blood glucose level of 80–95 mg/dL, and a postprandial blood glucose level <120 mg/dL. Both treatments caused significant reduction in blood glucose levels compared with levels measured at home for one week before initiation of treatment. Mean blood glucose levels in the glyburide group decreased from 114 to 105 mg/dL, whereas those in the insulin group decreased from 116 to 105 mg/dL. Eight-two percent of the glyburide and 88% of the insulin-treated patients achieved the desired level of glycemic control. Eight of the glyburide-treated women (4%) were transferred to the insulin therapy group. The two groups did not differ significantly in the rates of preeclampsia, cesarean section, and level of glycemia prior and subsequent to treatment. Additionally, no significant difference was found in the overall rates of small-for-gestational-age, macrosomia, ponderal index (>2.85), and the rate of perinatal complications between the groups. Furthermore, when patients were stratified by level of glycemic control to evaluate the impact of glycemia on the rate of abnormal fetal size, no difference was found between the two treatment groups but there was a significantly higher rate of large infants in the poor glycemic category. (Table 27-6) (Figure 27-4). There was no identifiable trend for one of the groups when all were nonsignificant. Furthermore, the 95% confidence interval (CI) for the difference of the mean was found to be relatively small, which suggests the unlikely possibility of beta errors. Of interest was

TABLE 27-3 Nonrandomized Studies

		Glyburide	Vs	Insulin	Good Control
Jacobson et al.[160]	Retrospective	137		122	86% vs. 63%
Holt et al.[161]	Retrospective	34		—	77%
Lim et al.[159]	Prospective observation	33		21	No Significant Difference
Conway et al.[155]	Prospective Observational	75		—	81%
Kremer et al.[154]	Prospective Observational	73		—	84%
Chmait et al.[87]	Prospective Observational	69		—	81%
Gilson et al.[153]	Prospective Observational	22		22	82%
Yogev et al.[156]	Retrospective	124		—	75%

TABLE 27-4 Randomized Trials: Oral Agents Compared to Insulin

		Oral	Insulin	Good Control
Langer et al.[20]	RCT	201 Glyburide	203	82% vs. 88%
Notelovitz et al.[38]	RCT	2 × 52 Tolbutamide Chlorpropamin	52	Oral 80%
Silva et al.[165]	RCT	32 Glyburide	36	Insulin 36%
Moore et al.[169]	RCT	31 Metformin	32	82%, ns
Rowen et al.[164]	RCT	363 Metformin	370	MBG-ns BG-ns
Anjalakshi et al.[171]	RCT	10 Glyburide	13	PP-ns
Bertini et al.[77,162]	RCT	24 Glyburide	27	79%
Silva et al.[166]	RCT	104 Glyburide	96	82%
Ogunyemi et al.[170]	RCT	48 Glyburide	49	HbA1c < in glyburide PP < in insulin
Spaulonci et al.[163]	RCT	47 Metformin	47	Lower mean in metformin group

Abbreviations: BG-ns, blood glucose, non-significant; MBG-ns, mean blood glucose, non-significant; PP-ns, post prandial, non-significant; RCT, randomized controlled trial.

TABLE 27-5 Effects of OHA Versus Insulin on Neonatal Outcome

	OHA	Insulin	WMD	95%CI
LGA	(103/628) 16.4%	(102/640) 15.9%	1.01	0.61–1.68
Neonatal hypoglycemia	(92/671) 13.7%	(90/685) 13.1%	1.59	0.70–3.62
Birth weight	3372 ± 501	3280 ± 543	56.11	–42.62–154.84
HbA1c (%)	5.5 ± 0.7	5.4 ± 0.6	0.1	–0.26–0.23
C/S	33%	36%	0.91	0.68–1.22

Abbreviations: C/S, cesarean section; WMD, weighted mean difference.
Favors OHA Favors Insulin.

Source: Modified from Dhulkotia et al.[146]

the finding that the results obtained in our randomized study were similar to the results obtained in our quasi-randomized intensified treatment study.[1] Furthermore, both studies had morbidity rates comparable to the normal population.

The Use of Metformin in Pregnancy

Metformin is a popular drug in the treatment of polycystic ovary syndrome (PCOS).[172] When these women become pregnant, the fetus is exposed to the drug during the first trimester. Thus, the physician is faced with two dilemmas: Should patients on metformin conceive while on the drug? When they do conceive, should the drug be stopped? The results of the studies revealed that in some cases the drug was stopped after conception while in others, the PCO patients remained on the medication. However, it must be emphasized that the majority of patients were pregnant but had no gestational diabetes. Therefore, pregnancy outcome in these patients cannot be compared to outcome in treated GDM women.

In a study by Glueck et al.[173] women with PCOS received metformin to reduce the occurrence of gestational diabetes.

TABLE 27-6 Selected Neonatal Outcomes

	Insulin ($n = 203$)	Glyburide ($n = 201$)	95% CI for Mean Difference
LGA (%)	12.8	12.4	–6.07, 6.87
Macrosomia (%)	4.0	7.0	–3.3, 8.68
Ponderal index >2.85 (%)	11.8	9.0	–3.3, 8.68
Hypocalcemia (%)	1.0	1.0	–1.94, 1.94
Hyperbilirubinemia (%)	3.9	5.5	–5.72, 2.53
Polycythemia (%)	2.5	1.5	–1.73, 3.73
IV Glucose (%)	11.0	14.0	–9.45, 3.45
Lung complications (%)	5.9	7.9	–6.94, 2.94
Respiratory support (%)	2.5	1.5	–1.13, 3.73
NICU (%)	7.4	5.9	–3.36, 6.36

Abbreviation: IV Glucose, intravenous glucose.

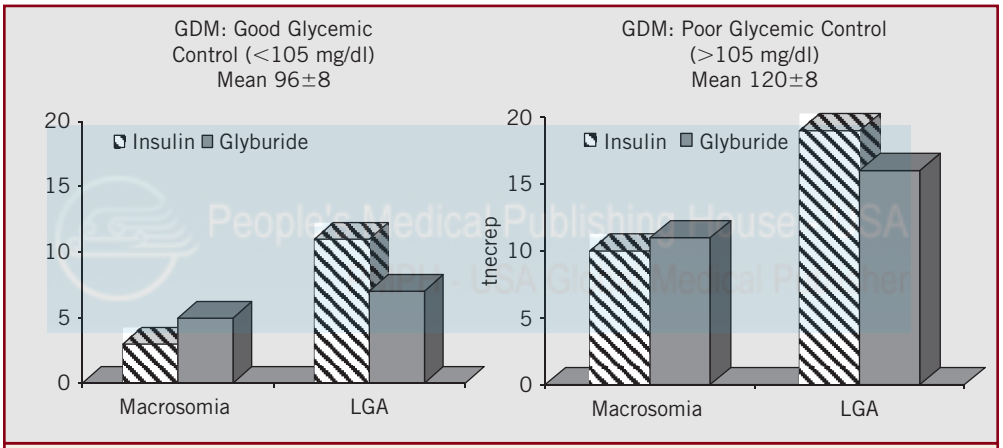

Figure 27-4 Pregnancy outcome by level of glycemic control.

Researchers found no evidence that the drug was teratogenic. Moreover, metformin reduced the likelihood of first trimester abortion by a factor of 10. In addition, the use of the drug in the preconception period reduced the incidence of GDM from 31% to 3%, a rate comparable to that found in the general population. No major fetal malformations or fetal hypoglycemic episodes occurred in the 34 live births, thus supporting Coetzee's findings.

However, in a study of 118 women with preexisting diabetes, Hellmuth et al.[174] found an incidence of preeclampsia of 32% in women treated with metformin, compared with 7% in the sulfonylurea group. Perinatal mortality was 11.6% and 1.3%, respectively. Other researchers did not replicate the researchers' findings. Of note, the sample size was relatively small in each arm of the study (metformin, insulin, diet, and sulfonylurea). The data also suggest that these patients were not maintaining optimal glucose control since there were similar high rates of macrosomia (35%) found in all treatment groups.

In a study of women with PCOS, metformin therapy decreased the rate of early pregnancy loss to 11%, compared with a rate of 58% among untreated women.[175] Although recent trials showed no adverse effect of metformin in terms of anomalies, no current study has evaluated pregnancy outcomes when patients were treated with the drug throughout gestation. Metformin and many other hypoglycemic and antihyperglycemic agents may in the future offer alternatives to glyburide with comparable or greater efficacy. However, current research has not provided the evidence for their safe use in pregnancy. Thus, glyburide is the only drug of choice at this time.

When treatment of diabetes was evaluated comparing insulin and metformin, similar findings to those with glyburide were found (Table 27-4). They determined that women with GDM are not associated with increased perinatal complications as compared to insulin.[162–164] However, the majority of the randomized and retrospective studies contained small sample sizes and, therefore, lacking at times the statistical power to present accurate results. Metformin was found to provide adequate glycemic control with lower mean glucose levels throughout the day, less weight gain, and a lower frequency of neonatal hypoglycemia.

Logistic regression analysis showed that gestational age at diagnosis and mean pretreatment glucose level were predictors of the need for supplemental insulin therapy in women initially treated with metformin.[163] Rowen et al.[164] in the largest randomized study to date evaluating metformin versus insulin reported that there was no difference between the two drugs for level of glycemic control and pregnancy outcome. However, 46.3% of the metformin group received insulin supplements throughout the study. This high percentage of patients receiving supplemental insulin may be due to a high rate of recruited women who were type 2 diabetics or alternatively that metformin treatment is less effective. Another study[37] compared patients treated with metformin and glibenclamide alone, and the combination of diet, metformin and glibenclamide. Patients who failed the OHA therapy were transferred to insulin therapy. The incidence of large-for-gestational-age (LGA) neonates was 15% in the metformin group, 27% among the glibenclamide users, 33% for combined therapy, and 41% for insulin. These varying rates are explained by differences in disease severity. Still, it is notable that subjects treated with metformin had the lowest rate. Neonatal hypoglycemia was defined as <25 mg/dL. The overall rate of neonatal hypoglycemia was 11.5%, with the highest rate for the patients treated with glibenclamide (27%) and the combination therapy (glibenclamide/metformin) 18%, compared to 5% in metformin-treated patients. The high rate of neonatal hypoglycemia corresponds with a rate of large infants reported in this study suggesting that a significant number of the patients were in suboptimal glucose control. Coetzee and Jackson[41,43] studied the effect of metformin as single or combination therapy in pregnancy demonstrating a significant mean decline in plasma glucose concentrations. In one study, the failure of metformin to achieve the targeted level of glycemic control was 53.8% in women with established diabetes and 28.6% in women with gestational diabetes.[43] Apart from a high incidence of neonatal jaundice requiring phototherapy, infant morbidity in the metformin group was low. The rate of LGA infants was double the rate found in the authors' general population. However, the LGA rate was comparable in the metformin and insulin-treated patients, approaching 20%. Finally, in this study, the mothers of the three infants with congenital malformations in the metformin group initiated therapy in the third trimester.

Systemic review suggested that no substantial maternal or neonatal outcome differences were found with the use of glyburide or metformin compared with the use of insulin.[176] The question now remains, should glyburide or metformin be the drug of choice as the alternative to insulin? There is paucity of information regarding this query. One small randomized study[165–167] (n = 40 metformin and n = 32 glyburide) reported no difference in treatment failure for fasting and postprandial plasma glucose as well as rate for LGA and newborns with hypoglycemia. In contrast, Moore et al.[168,169] in a randomized study of 74 glyburide and 75 metformin patients reported that 34.7% in the metformin and 16% in the glyburide group did not meet the glycemic goals and required insulin therapy. The glycemic goal in the study was fasting blood glucose <105 mg/dL or two-hour postprandial of <120 mg/dL. The failure rate of metformin was 2.1 times higher than the failure rate of glyburide (95% CI 1.2–3.0, odds ratio 2.7). Of the patients who achieved glycemic control on either medication, there was no difference in mean fasting or two-hour postprandial blood glucose values between the two treatment arms.

Is Glyburide as Effective as Insulin in All GDM Severity Levels?

Our study demonstrated[177] that glyburide and insulin were equally efficacious in the treatment of GDM at all severity levels. Over 80% of GDM patients requiring pharmacological intervention will achieve the established levels of glycemic control with glyburide. The majority of patients (71%) will require, on average, up to 10 mg daily dose of glyburide to achieve established levels of glycemic control. We further demonstrated that in all GDM severity levels, the success rate for achieving glycemic goals is similar in insulin- and glyburide-treated patients. However in general, as the level of disease severity increases, the success rate for achieving glycemic control decreases. Moreover, the majority of patients can be successfully treated with a 2.5–10 mg/daily dose of glyburide. In our previous study[20] a small number of glyburide-treated subjects were transferred to insulin therapy. A significantly higher rate of maternal hypoglycemic episodes was found in the insulin versus the glyburide group. In a follow-up study[143] using continuous blood glucose monitoring, we again confirmed our original findings. Similar results were demonstrated in our studies[144] and meta-analyses.[145,146]

When patients were stratified by level of GDM severity, no significant difference was found in neonatal size, metabolic complications, and composite outcome variables between the two treatment modalities.[177] Finally, a logistic regression analysis revealed that overall, mean blood glucose determination, GDM severity (categorized by the fasting plasma from the oral glucose tolerance test), previous macrosomia and weight gain in pregnancy were the only significant contributors associated with increased risk for adverse outcome in pregnancy. Treatment modality was not a contributing risk for adverse outcome. Since the recommended threshold for initiation of pharmacological therapy is fasting plasma glucose >95 mg/dL and/or two-hour postprandial value >120 mg/dL, it follows that for the majority of patients, glyburide therapy can be the drug of choice when diet treatment fails. Glyburide and insulin are equally efficient for treatment of GDM at all levels of disease severity. Achieving the established level of glycemic control, not the mode of pharmacological therapy, is the key to improving the outcome in GDM pregnancies.

When diet and pharmacological therapies are initiated, the success rate is rarely 100%. In fact, success rates in monotherapy will be lower than in combination therapies. For example, current hypertension therapy recommends a combination of two to three drugs to maximize the success rate. Moreover, success rate varies depending upon GDM severity, type 2 diabetes and at times, medication preference. Of the approximately 20% of glyburide-treated women who fail to achieve glycemic control, will transfer to insulin therapy alter the outcome? At the same time, even with those who fail to achieve the goals, they may benefit more from an early planned delivery than the addition of another drug (depending upon gestational age). Several studies sought to address this issue.[87,155,156,178–180] The studies showed similar success rates when glyburide was initiated as a monotherapy ranging from 81% to 84%. When level of glycemic control was reevaluated in the subgroup of patients who failed to achieve goals and

TABLE 27-7 Can Success Rate be Predicted With Transfer of Patients to Insulin Therapy?

	No.	Fasting	1st Success	Transfer Failure
Conway et al.[155]	12/75	115 ± 24	84%	67% (8/12)
Chmait et al.[87]	13/69	≥126	81%	–
Rochon et al[179]	21/101	107 ± 15	79%	–
Kahn et al.[158]	18/95	112 ± 24	81%	55% (10/18)
Yogev[156]	31/124	94 ± 14	75%	54% (17/31)
Langer[180]	38/700	99 ± 22	76%	55% (21/38)

transferred to insulin, the failure rate ranged from 54% to 67%. This finding revealed that even when transferred, the majority of patients still did not achieve glycemic targets (Table 27-7).

How Is Selection of Pharmacological Therapy Influenced by Maternal Weight?

The majority of individuals with GDM and type 2 diabetes are overweight or obese.[181] Although insulin resistance is thought of as the predominate driver of diabetes in obese patients, these women actually have a similar degree of islet dysfunction to leaner patients.[182] Perhaps as a result, the obese may be more likely to require combination drug therapy. Although common practice has favored metformin in heavier patients, because of weight loss/weight neutrality, this drug is efficacious in lean individuals. We showed in the past that insulin therapy is superior to diet therapy in GDM subjects and should be the initial therapy provided. Would glyburide be as effective as insulin for these patients? We found that glyburide is as successful as insulin with no significant differences in pregnancy outcome (Table 27-8).[183]

Oral Antidiabetic Drugs and Lactation

There are numerous factors that influence the transfer of drugs into breast milk.[184] One factor is the degree of protein binding that will determine if and how much of the drug will cross from maternal plasma to the milk. Only free drugs can pass from the maternal plasma into milk. In addition, the volume of drug distribution in the mother and the difference in pH between maternal plasma and breast milk will determine the degree of transfer. Although insulin does not cross into the breast milk, less is known about oral antidiabetic drug agents. Acarbose and troglitazone (since withdrawn from the market because of its link with fatal liver failure) are potentially good choices of oral agents for glucose control in lactation. There is evidence that first-generation sulfonylureas (chlorpropamide and tolbutamide) transfer into breast milk. Although glipizide and glyburide (glibenclamide) are highly protein-bound, they have small amounts of distribution that may indicate passage into breast milk. Two large centers in Canada and California that examine drug safety have separately demonstrated that glyburide does not cross into breast milk.

Since metformin has a non-protein-binding capacity, it should in all likelihood transfer into the milk. However, studies demonstrated[185,186] that the concentrations of metformin in breast milk were generally low and the mean infant exposure to the drug was only 0.28% of the weight-normalized maternal dose. As this is well below the 10% level of concern for breast-feeding, and because the infants were healthy, the authors concluded that metformin use by breast-feeding mothers is safe.

TABLE 27-8 [a]Obese Gestational Diabetic Women: Comparison of Insulin and Glyburide Therapies

	Insulin (%)	Glyburide (%)
Composite	50.7	44.3
Macrosomia	5.6	6.3
LGA	16.7	13.9
Ponderal Index	13.2	13.5
Metabolic complications	9.6	14.1
Respiratory	8.7	11.8
Cesarean section	25	20.3

[a]All nonsignificant.
Source: Langer, O, et al. 2006.[183]

Cost of Glyburide and/or Metformin Therapy Compared to Insulin

Oral antidiabetic medications such as glyburide and metformin are being used increasingly in women with GDM, although not yet approved by the Food and Drug Administration. These drugs are especially attractive since in GDM the relative abnormal profile is lower than in either type 1 or type 2 diabetes. The oral administration drugs are patient friendly and achieve the same success rate as insulin. Cost analysis showed that glyburide is less costly than insulin for the treatment of GDM. Cost models can be useful to physicians deciding between two equally effective medications, allowing them to incorporate information about their individual practice styles with a complex balance of cost implications.[187,188] In light of current questionable health-care dollars and the needs of underdeveloped countries, this alternative to insulin bodes well for effective and efficient treatment for more women.

SUMMARY

The successful treatment of GDM with oral agents as an alternative to insulin therapy is an actuality. Sufficient data generated through rigorous studies in the past decade have made this

alternative for care a reality. A multitude of women have been treated with either glyburide or metformin with major success. The drugs are user friendly, cost effective, and have been shown to be as effective as insulin therapy. The Hippocratic Oath requires that the physician do no harm. However, this is a double-edged sword: providing medication that has not been rigorously tested can cause harm. But, on the other hand, denying women medication that has been meticulously tested also causes harm. We as physicians should not have to choose between what is right or wrong but *what is more right*.

The true currency of science, after all, is not faith or even truth, but doubt. Therefore, nothing is sacred. Take evidence-based medicine, all the rage in the new age of health care. The basis for it can impede medical progress by discouraging doctors from trying alternative treatments based on "expert" opinions or because the medication has not been "blessed" by randomized controlled trials. One needs to remember that many patients suffer from more conditions than experiments can control for. In science everything has to be questioned. When clinicians and research scientists stop bickering, then we will know we are in trouble.

The current journey and rites of passage for the use of oral antidiabetic drugs, especially glyburide for clinical use in pregnancy can be best summarized:

When it's new, people say it's not true;
Later, when it becomes true,
People say it's not new.

– Voltaire

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The Role of Polycystic Ovary Syndrome: Management of Type 2 and Gestational Diabetes Mellitus

28

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Happy are those who dream dreams and are ready to pay

the price to make them come true.

—Leon Suenes

Key Points

- Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among women of reproductive age, associated with reproductive and metabolic dysfunction
- PCOS is associated with increased risk of impaired glucose tolerance (IGT) and type 2 diabetes (T2D)
- PCOS women are at increased risk for adverse pregnancy outcomes, that is, gestational diabetes mellitus (GDM), pregnancy-induced hypertension (PIH), preeclampsia, and preterm birth
- Metformin does not improve live birth rates in PCOS patients undergoing infertility treatment and should therefore be restricted for only those with IGT
- Although metformin does not improve pregnancy outcome in nonhyperinsulinemic PCOS patients, a beneficial effect was demonstrated in those with IGT

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy among women of reproductive age, associated with reproductive and metabolic dysfunction.[1] The clinical presentation varies from eumenorrhea and a sonographic picture of polycystic ovaries but with subtle phenotypic abnormalities or signs of hyperandrogenism, to advanced Stein and Leventhal syndrome[2] with clinical heterogeneity as the rule. Moreover, most women with PCOS also exhibit features of the metabolic syndrome, including impaired glucose tolerance (IGT), obesity, and dyslipidaemia[3–5] with their associated long-term sequelae namely endometrial carcinoma, hypertension, type 2 diabetes (T2D), and cardiovascular disease.

The pathophysiology of PCOS is not completely understood and its etiology remains an enigma. Moreover, until 2004, there was no single acceptable definition, though the most widely used indicator is the presence of typical ultrasound features of the polycystic ovaries[6] in association with hyperandrogenism and/or chronic anovulation in women without specific underlying disease of the adrenal or pituitary glands. The recognition of the controversies surrounding the diagnostic criteria of PCOS has led to the Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group that revised the diagnostic criteria and addressed the long-term health risks related to PCOS.[1] The Rotterdam ESHRE/ASRM PCOS consensus recommended that PCOS be defined when at least two of the following three criteria are present: (1) polycystic ovaries, (2) oligo and/or anovulation, and (3) clinical and/or biochemical signs of hyperandrogenism. Accordingly, the estimated prevalence of PCOS varies from 3% to 20% depending on the diagnostic criteria used.[7]

PCOS, IGT, AND T2D

IGT, or insulin resistance, are defined as decreased insulin-mediated glucose utilization. It has long been recognized as a major risk factor for diabetes.[8] Moreover, it was shown that lifestyle intervention or metformin in patients with IGT may reduce the prevalence of T2D.[9]

The cellular and molecular mechanisms of insulin action in PCOS have been widely investigated. It was demonstrated that insulin-dependent receptor tyrosine autophosphorylation was significantly decreased, while insulin-independent receptor serine

phosphorylation was markedly increased resulting in normal receptor signaling inhibition.[10,11] This increased insulin-independent serine phosphorylation in PCOS insulin receptors appears to be a unique disorder of insulin action, not presented in other insulin-resistant states such as T2D, obesity, and so forth.[10,12] and acts synergistically with obesity to detrimentally affect insulin action.[13]

Several dynamic invasive tests and calculated indices are currently available for detecting IGT. Although the euglycemic clamp technique is considered the most accurate test for the assessment of insulin resistance, this cumbersome test is frequently replaced by the simple measurement of the ratio of fasting glucose to fasting insulin, or the two-hour glucose level after a 75-g oral glucose tolerance test (OGTT) (WHO criteria, IGT > 140–199 mg/dL).[14] As a result, reports of the prevalence on IGT in women with PCOS vary depending on the sensitivity and specificity of the tests employed and the heterogenic phenotypes of PCOS.

There is now convincing evidence that PCOS is associated with increased risk of IGT and T2D.[15,16] Studies published before the 2003 Rotterdam ESHRE/ASRM PCOS consensus on diagnostic criteria for PCOS have reported 23%–35% and 4%–10% prevalence for IGT and T2D, respectively, in PCOS women.[17–19] Moreover, the prevalence of IGT and T2D were respectively 2- to 3-fold and 7.5- to 10-fold, higher in PCOS compared to age- and weight-comparable to reproductively normal control women.[17,18]IGT was mainly evident in post-glucose challenge glucose levels and the prevalence was highest in obese affected women; lean PCOS women showed increased rates of IGT and T2D.[17] Similar figures were also observed following the 2003 Rotterdam ESHRE/ASRM PCOS consensus. Moran et al.[15] in their comprehensive meta-analysis have demonstrated that PCOS women had increased prevalence of IGT (odds ratio [OR] 2.48), T2D (OR 4.43), and metabolic syndrome (OR 2.88) as compared to body mass index (BMI)–matched controls. Moreover, using the gold standard clamp techniques, Stepto et al.[20] have recently confirmed that PCOS women, irrespective of BMI, are more IGT and report that the prevalence of IGT in PCOS based on the World Health Organization (WHO) definition (<25th centile of glucose infusion rate in healthy lean controls) is 75% in lean PCOS, 62% in overweight controls, and 95% in overweight PCOS in a largely Caucasian population.

The different phenotypes of PCOS present similarities but also important differences in their clinical and endocrine pattern. Although the risk of IGT or diabetes is highest in women who have both oligo/anovulation and hyperandrogenism and is further amplified by obesity,[21] most of the normoandrogenic PCOS do not exhibit the two main components of PCOS: hyperandrogenism and IGT.[22,23]

PCOS AND ADVERSE PREGNANCY AND NEONATAL COMPLICATIONS

Women with PCOS, who desire a pregnancy may be at increased risk for adverse pregnancy outcomes. This may be exacerbated by obesity and/or IGT (Amsterdam). Boomsma et al.[24] have conducted a meta-analysis aiming to evaluate the risk of pregnancy and neonatal complications in women with PCOS. Of the 15 eligible studies, involving 720 PCOS women and 4505 controls, PCOS women demonstrated a significantly higher risk of developing GDM (OR 2.94), PIH (OR 3.67), preeclampsia (OR 3.47), and preterm birth (OR 1.75). Moreover, their babies had a significantly higher risk of admission to a neonatal intensive care unit (NICU) (OR 2.31) and a higher perinatal mortality (OR 3.07). These observations were recently confirmed by Qin et al.[25] evaluating 27 studies involving 4982 women with PCOS and 119,692 controls. They also demonstrated a significantly higher risk of developing GDM (OR 3.43), PIH (OR 3.43), preeclampsia (OR 2.17), preterm birth (OR 1.93), and caesarean section (OR 1.74) in PCOS patients compared to controls. Moreover, PCOS babies had a marginally significant lower birth weight and higher risk of admission to NICU compared to controls. They, therefore, concluded that women with PCOS should be followed closely during pregnancy and parturition in an attempt to prevent or ameliorate these complications.

Pregnancy-associated risks are greater in women diagnosed by more classic National Institute of Health (NIH) criteria as opposed to nonhyperandrogenic women.[26] This probably reflects the well-known observation that PCOS phenotypes had different hormonal and metabolic patterns, in particular, a full-blown phenotype associated with IGT in contrast with the ovulatory phenotype.[23,27,28] In their prospective controlled study, Palomba et al.[29] evaluated the clinical impact of the main features of PCOS in 97 pregnant PCOS women and 73 healthy pregnant controls. The relative risk for adverse obstetric or neonatal outcomes was increased in PCOS patients and varied according to the PCOS phenotype, as defined by the ESHRE/ASRM consensus on PCOS diagnostic criteria.[1] They observed a higher relative risk for adverse outcomes in patients with the full-blown and non-PCO phenotypes than in those with the nonhyperandrogenic and ovulatory phenotypes (1.93, 2.23, 0.54, and 0.48, respectively). The risk for adverse obstetric or neonatal outcomes was affected significantly by ovarian dysfunction and biochemical hyperandrogenism, whereas no significant effect was detected for clinical hyperandrogenism and PCO.

METFORMIN FOR PCOS PATIENTS

Women with the PCOS are at increased risk for the metabolic syndrome and its associated health risks.[26] One of the cardinal components of metabolic syndrome is insulin resistance and its compensatory hyperinsulinemia, which are considered prominent features of PCOS and have a cardinal role in the pathophysiology of the syndrome.[30]

Metformin, an orally active biguanide, enhances insulin sensitivity by the inhibition of hepatic glucose production and by increasing glucose uptake and utilization into muscle tissue. It has been commonly used for the treatment of T2D. Moreover, for approximately two decades, metformin has been also used in PCOS patients to improve insulin resistance and reduce hyperinsulinemia with the subsequent improvement in PCOS metabolic and hyperandrogenic disturbances.[31,32]

With regard to its use during pregnancy, according to the Federal Drug Administration, metformin is a category B drug. This means that either animal studies have shown an adverse effect not confirmed by controlled studies in women, or animal studies have not shown a fetal risk but there are no controlled studies in women. A systematic review and meta-analysis conducted by Gilbert et al.[33] based on eight small eligible studies

revealed that metformin treatment in the first trimester does not appear to be unsafe for use during pregnancy with respect to major malformations.

Prompted by the aforementioned observations, subsequent studies reported the beneficial effects of metformin on ovulation rate,[32] abortion rate,[34] and improvement of pregnancy outcome[35] in PCOS patients.

METFORMIN AND INDUCTION OF OVULATION

PCOS women with insulin resistance undergoing ovulation induction with gonadotropin have a longer duration of treatment, use a higher total follicle-stimulating hormone (FSH) dose, and have an elevated cancellation rate and a lower conception rate.[36,37]Improving insulin sensitivity through both lifestyle and pharmacological intervention were suggested to ameliorate the aforementioned abnormalities, restore ovulation, and enhance pregnancy in women with PCOS.

However, a systematic review by Costello et al.[38] demonstrated that although the coadministration of metformin to gonadotropin ovulation induction and in vitro fertilization (IVF) does not improve ovulation, pregnancy, or live birthrates, it does consistently affect ovarian response during ovulation induction with variable effects on the length of ovarian stimulation, total dose of FSH used, peak serum E_2 level, the number of oocytes collected, and reduces the risk of ovarian hyperstimulation syndrome. Following two randomized controlled studies that could not demonstrate an increase in live birthrate with metformin as compared to clomiphene treatment for ovulation induction,[39,40] a recently published ESHRE/ASRM consensus,[41] that addressed the therapeutic challenges raised in women with infertility and PCOS, concluded that there is no evidence for improved live birthrates with the use of metformin, and metformin should be, therefore, restricted only to those patients with glucose intolerance.

METFORMIN AND SPONTANEOUS ABORTION

The associations between abortion or malformations and poor glycemic control in the periconceptional period are well established.[42] According to the Amsterdam ESHRE/ASRM consensus, miscarriage rates are not increased in natural conceptions in women with PCOS, independent of obesity, while after induction of ovulation, the rate mirrors those found in other infertile populations.[26] However, in most of the published studies, miscarriage rates were significantly higher in PCOS patients who had one or more pregnancies (44%) or in those conceiving following IVF treatment (35.8%),[29,43,44] and appeared to be threefold higher compared to controls.[45]

The suggested mechanisms by which PCOS could cause miscarriage are hypersecretion of luteinizing hormone (LH); elevated androgen concentrations, which may lead to abnormally developed endometrium; reduction in endometrial glycodelin A expression and its known detrimental effect on oocyte quality/embryo viability; and hyperinsulinaemia with the consequent decrease in serum glycodelin and insulin-like growth factor-binding protein-1 levels, and elevation in plasminogen activator inhibitor-1 (PAI-1) and homocysteine concentrations (summarized by Cocksedge et al.[46]).

Considering the potential beneficial effects of metformin, which was shown to reduce body weight, LH, androgens, and PAI-1 levels (summarized in Palomba et al.[47]), it was offered to PCOS patients, in an attempt to prevent abortions to increase uterine blood flow,[48] and to reduce insulin resistance and hyperinsulinaemia that protect against development of miscarriage, as was already established in pregestational diabetic patients undergoing strict euglycemic control.

However, data related to metformin and abortion risk are conflicting.[49,50] When the miscarriage rate was compared in the same group of PCOS women before and after metformin therapy, the reported reduction in miscarriage rates ranged from 62%–73% to 8.8%–26%.[34,51,52]

Moreover, a closer analysis of the data reveals that the majority of the available studies are observational, uncontrolled, and of short duration and women were not necessarily selected or tested for hyperinsulinemia. For example, in Palomba et al.[49] meta-analysis, of the 17 eligible studies, in only three studies were patients insulin resistant. In these results, 2 out of 16 (8%) of women aborted in the metformin arm versus 3 out of 16 (18.8%) in the control; these small sample sizes make it impossible to draw reasonable conclusions.

METFORMIN AND PREGNANCY COMPLICATIONS

As described above, PCOS women are at increased risk for adverse pregnancy outcomes, that is, GDM, PIH, preeclampsia and preterm birth. In women with GDM, no differences were seen between metformin- and insulin-treatment groups at different levels of glucose control. Moreover, metformin (alone or with supplemental insulin) was not associated with increased perinatal complications as compared with insulin.[53,54]

Metformin administration to PCOS patients during pregnancy was suggested to reduce the risk of gestational diabetes.[35,52] Among PCOS patients receiving metformin, only 3%–4% were reported to develop gestational diabetes compared to 26%–27% in their previous untreated pregnancies.[35,52] However, while in De Leo et al.[55] study of hyperinsulinemic overweight PCOS patients, metformin eliminated gestational diabetes, in the randomized, placebo-controlled, double-blind, multicenter study by Vanky et al.[56] of 274 singleton pregnancies, receiving either metformin or placebo, the prevalence of GDM was17.6% versus 16.9%, respectively. Of note, in contrast to the study by De Leo et al.,[55] according to patients mean fasting and two-hour glucose levels, patients in the Vanky et al.[56] study were not hyperinsulinemic with the consequent relatively low prevalence of GDM. Therefore, Vanky et al.[56] observations cannot reflect the preventive role of metformin in insulin-resistant PCOS patients, as shown elsewhere.[57,58]

Since metformin modulates blood pressure, lipid profile, insulin resistance, and fibrinolytic activity, it is reasonable to assume that it may prevent PIH.[59] Glueck et al.[60] have prospectively compared the prevalence of preeclampsia in metformin-treated PCOS women to healthy controls. No difference was observed between the two groups (5.2% vs. 3.6%, respectively). In the study by De Leo et al,[55] none of the PCOS women treated with metformin developed hypertensive disorders or preeclampsia while the gestational hypertension was demonstrated in 11% ($P < 0.05$) and preeclampsia in 3% ($P = 0.24$) of the control

group. Again, in Vanky et al.[56] study of noninsulin-resistant PCOS patients, preeclampsia prevalence was 7.4% in the metformin group and 3.7% in the placebo group. These observations confirm the protective role of metformin against PIH in insulin-resistant pregnant PCOS patients, presumably due to the aforementioned beneficial effects and its ability to induce weight loss and to control weight gain during pregnancy.

SUMMARY

PCOS is the most common endocrinopathy among women of reproductive age associated with reproductive and metabolic dysfunction. PCOS phenotypes have different hormonal, metabolic, and clinical patterns, some of which are at increased risk of IGT and T2D. PCOS women are also at increased risk for adverse pregnancy outcomes, that is GDM, PIH, preeclampsia, and preterm birth that may be ameliorated by metformin administration.

In our practice, we screen all PCOS patient for IGT by fasting glucose to insulin ratio and 75-g OGTT. Metformin is offered only to insulin-resistant PCOS patients starting at a dose of 850 mg bid preconceptionally.

According to the Thessaloniki ESHRE/ASRM PCOS Consensus Workshop Group, decisions about continuing metformin during pregnancy in women with glucose intolerance should be left to obstetricians providing care and based on a careful evaluation of risks and benefits.[41] Two commonly used protocols are either to stop metformin with pregnancy confirmation or to continue metformin throughout the first trimester and then to halve the dose and continue metformin up to the 37th week of gestation.

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PART IV Pregnancy Complicated by Pre-existing Diabetes

Preconception Care in Diabetes: Shortcomings and Challenges

29

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Planning is bringing the future into the present so that you can do something about it now; it pays to plan ahead. It wasn't raining when Noah built the ark.

—Robert Cushing

Key Points

- Diabetes is a global disease requiring global efforts at deploying preconception care
- Maternal and fetal complications of diabetic pregnancy are reducible with preconception care
- Effective preconception care of women with diabetes requires meticulous glycemic control, normalization of body mass index (BMI), and provision of folic acid supplements
- Significant social, economic, and personal barriers to preconception care can be reduced through coordinated, multidisciplinary care and health policy initiatives

THE GLOBAL CHALLENGE OF PRECONCEPTION CARE IN DIABETES

Worldwide 1 in 10 pregnancies may be associated with diabetes. At present, an estimated 347 million people worldwide have diabetes and more than half of these are women. At least one-third of these, some 60 million globally, are of reproductive age, who will embark on pregnancies with suboptimal glucose control, which in turn will place their fetuses and newborns at significant short-term and lifetime risk. Moreover, the longitudinal trends in diabetes prevalence are discouraging, with an emerging global epidemic of diabetes that can be traced to burgeoning overweight, obesity, and physical inactivity.[1]

In the United States, a similarly alarming problem has evolved. In 2010, there were 22 million persons with diabetes in the reproductive ages of 20–39 years and an additional 54 million had impaired glucose tolerance or "prediabetes" with the potential to develop fetal and maternal morbidities of hyperglycemia during pregnancy. Further, the startling upswing in the prevalence of diabetes in the United States is exclusive due to increasing rates of type 2 diabetes.[2] Thus, if preconception care of women with diabetes is to be effectively applied, a major redirection of medical and social resources will be necessary.

THE MORBIDITIES OF DIABETES DURING PREGNANCY IN WOMEN WITH POOR GLYCEMIC CONTROL

It has long been recognized that preexisting diabetes poses special risks for both mother and fetus if glucose is not well controlled in the first trimester. Specifically, the occurrence of fetal structural anomalies increases severalfold and these include disorders of the nervous, cardiovascular, gastrointestinal, and renal systems, as well as skeletal anomalies. Estimates of the increases in fetal malformations typically are in the three to four times range, with central nervous system malformations almost doubled, cardiac malformations increased 20% to 30%, and renal and skeletal abnormalities severalfold. A recent study by Guerin[3] in 2007 demonstrated a curvilinear relationship between preconception hemoglobin A1c (HbA1c) and the incidence of congenital anomalies. With an HbA1c of 6.9 or less, the incidence of birth defects was approximately 2.5%, almost equivalent to the nondiabetic population. However, in women beginning pregnancy with HbA1c above 10%, the risk of congenital anomalies was elevated by three- to fourfold in the 6%–7% range. For women whose HbA1c exceeded 13%, as many as one in seven fetuses had a congenital anomaly. Most of these malformations occur in the first trimester and thus typically coincide with or precede maternal recognition of pregnancy. Even in the most adept clinical hands, women whose diabetes is suboptimally controlled prior to conception will rarely achieve adequate control by mid embryogenesis to normalize the risk of fetal malformations.

Other hazards for the fetus and newborn associated with maternal pregestational diabetes include excessive fetal fat accretion, progressive of remodeling of the fetal heart (interventricular septal hypertrophy), intermittent hypoxia associated with unchecked glucose excursions, and an increase in stillbirth. For those who reach the late third trimester, the perils of labor and delivery are substantial as fetal tolerance for the oxygen reductions associated with uterine contractions is poor. And, because

fetal fat accretion increases thoracic and abdominal girth but does not affect cranial dimensions, fetus is at increased risk for shoulder dystocia and neurologic injury.

The incidence of these morbidities is directly proportional to maternal glycemic control. Langer et al.[4] in 1991 estimated the risk of shoulder dystocia to be approximately 2.5% among babies with birth weight of 4000 g for both normoglycemic and diabetic gravidas, whereas among babies weighing 4500 g, the risk of shoulder dystocia was almost tripled if the mother had diabetes.

Thus, it appears that since most of fetal adipose accretion and cardiovascular stress occurs in the second and third trimesters, it may be possible, without preconception diabetes care, to avoid these complications. However, a patient who has been chronically accustomed to maintaining glucose values well above the normal range rarely is able to control her blood sugars in the critical second and third trimesters adequately to avoid substantial fetal fat accretion. A better approach would be to delay pregnancy until maternal glucose control is optimized for fetal well-being.

THE BENEFICIAL EFFECTS OF PRECONCEPTION CARE FOR PREGESTATIONAL DIABETES

The benefits of preconception care were established by Fuhrmann et al.[5] in 1983, documenting a cohort study that demonstrated fetal malformations in only 0.8% of women attending a preconception care clinic as opposed to a 7.5% rate in those who did not. Table 29-1 demonstrates a comparison of five studies of preconception care summarized by Temple.[6] With preconception care, the mean malformation rate was substantially lower (crude mean 1%) than among those who had usual care (crude mean 6.7%), yielding a net reduction of 86% (range 70%–100%). This marked difference in the malformation rates is associated with a strikingly modest reduction in HbA1c (crude mean 17%, range 9%–29%) occurring prior to conception. In aggregate, these studies demonstrate the utility of preconception care for avoiding congenital malformations in women with pregestational diabetes.

The value of a preconception care clinic has been assessed in a number of randomized controlled trials, 11 of which were recently summarized in a meta-analysis by Wahabi et al.[7] in 2010. Preconception care was associated with a significant reduction in prepregnancy HbA1c, a 75% reduction in congenital anomalies and perinatal mortality was similarly reduced by 65%.

The utilization of preconception care in medical clinics of the National Health Service among women with pregestational diabetes was evaluated by the Confidential Enquiry Into Maternal and Child Health (CEMACH) in 2007 in the United Kingdom.[8] In this extensive assessment, it was demonstrated that among women with type 1 diabetes, preconception counseling occurred in only 38% and glucose assessments in only 40%. Only 40% were taking folic acid supplements. Among women with type 2 diabetes, the figures were more discouraging with preconception counseling occurring only in 25% and glucose assessment in 30%. Given that these results were obtained in a country with universal health insurance, there is little reason to believe that statistics derived from the experience of women in the United States is better.

The problem of providing preconception care has been further complicated recently by the emergence of an epidemic of obesity. As demonstrated by Anderson et al.[9] in a large case–control study after adjusting for maternal ethnicity, age, education, smoking, alcohol use, and periconceptional vitamin use, obese women had substantially increased risks of delivering offspring with anencephaly (odds ratio = 2.3; 95% confidence interval [CI] 1.2–4.3), spina bifida (2.8; CI 1.7–4.5), and isolated hydrocephaly (2.7; CI 1.5–5.0). Odds ratios were higher for the joint effects of maternal obesity and maternal diabetes.

Similarly, Martinez-Frias et al.[10] also noted that the increase in congenital birth defects occurring in pregnancy with diabetes is potentiated by coexisting obesity. Whereas nonobese women with diabetes had congenital malformation rates near those of nondiabetic controls (approximately 2%) in obese diabetic women (body mass index [BMI] above 30) had malformed fetuses in the 4%–5% range. Thus, although it may have been considered formerly that women with mild degrees of type 2 diabetes may be at

TABLE 29-1 Studies Comparing Outcomes of Women with Diabetes Receiving Preconception Care (PCC) to Those Entering Pregnancy without Preconception Care

Author	Reference	PCC HbA1c	No PCC HbA1c	Percent HbA1c Reduction	PCC Malformation (%)	No PCC Malformation (%)	Percent Malformation Reduction
Goldman et al.	22	7.4	10.4	29	0.0	9.6	100
Steel et al.	23	8.4	10.5	20	1.4	10.4	87
Rosenn et al.	24	8.5	9.9	14	0.0	1.4	100
Temple et al.	25	6.6	7.6	13	1.8	6.1	70
Murphy et al.	26	6.9	7.6	9	1.8	6.1	70
Crude Mean		7.56	9.2	17	1.00	6.72	86

somewhat less risk of congenital anomalies, the overlay of obesity multiplies the risk significantly.

The task of providing preconception care to women with gestational diabetes in a prior pregnancy, who did not complete postpartum metabolic testing and are therefore at risk of entering a next pregnancy with significant hyperglycemia, continues to be challenging.

PRECONCEPTION CARE: IS GLUCOSE CONTROL ENOUGH?

Multiple studies have demonstrated the value of the folic acid supplementation in reducing congenital anomalies in pregnant women. Carea Villasenor[11] in 2003 catalogued a decade-long and progressive drop in spina bifida rates in the Baltimore, Maryland area. Not until fortification of food and increased emphasis on vitamin supplementation in doctors' offices was initiated, did the rate drop further. Among women with diabetes, the effects of folic acid in the reduction of congenital anomalies are even more impressive. When nondiabetic women taking supplemental vitamins are compared to women with diabetes not taking supplemental folic acid, the odds ratio for cardiac defect was 13.35, whereas if women with diabetes took supplemental folic acid, the odds ratio of the malformed infant dropped to 5.5.[12]

PRECONCEPTION CARE: CURRENT RECOMMENDATIONS

The American College of Obstetricians Gynecologists (ACOG) Practice Bulletin Number 60, 2005 Pregestational Diabetes Mellitus,[13] recommends preconception counseling for all women with pregestational diabetes, which should include discussion of potential vascular complications occurring during pregnancy (ophthalmic, renal, cardiovascular). Because of the link between thyroid dysfunction and diabetes, assessment of thyroid function is recommended and 400 μg daily folic acid supplementation is advised with the proviso that it could be possibly higher. It is notable the contraception is not mentioned in that Practice Bulletin.

The American Diabetes Association (ADA) recommendations for preconception care of women with diabetes published in 2012[14] endorsed incorporation of preconception counseling in routine diabetes clinic visits for all women of childbearing potential. They recommend that HbA1c level should be maintained as close to normal as possible (less than 7%) before conception is attempted. They also recommend that women with diabetes contemplating pregnancy should be evaluated and treated as indicated for vascular complications of diabetes, discontinuance of medications that may pose risk to the fetus including statins, angiotensin-converting enzyme inhibitor (ACE) inhibitors, ARBs, and most noninsulin therapy. Also notable in the ADA standards is the absence of recommendations regarding the role of contraception.

EFFECTIVENESS OF PRECONCEPTION CARE FOR WOMEN WITH DIABETES

The status of preconception care delivered in the medical clinics of the British National Health Service was assessed in 2007 with the CEMACH study, which was summarized recently by Temple.[6] Among the principal findings of the study were the following:

- Lack of preconception care was associated with a fivefold increase in adverse pregnancy outcomes.
- Only 17% of the medical units that participated in the survey, all of which were actively providing care to women with diabetes, actually provided multidisciplinary preconception care to women.
- Regarding women with type 1 diabetes, fewer than half received prepregnancy counseling (39%), folic acid supplements (43%), or achieved a HbA1c less than 7% (35%).
- Regarding women with type 2 diabetes, the percentage receiving preconception care was significantly less with only 25% receiving prepregnancy counseling and only 29% taking folic acid.

The CEMACH study also assessed the attributes of women whose pregnancies were planned versus those that occurred unplanned. A critical feature associated with having a planned pregnancy was having a positive relationship with the preconception health-care team that provided encouraging and empowering prepregnancy advice as opposed to health-care teams providing discouraging and negative views of a potential pregnancy.

A U.S. study by Perritt et al.[15] utilizing the Pregnancy Risk Assessment Monitoring System, assessed contraception use among women with preexisting medical problems. Whereas 50%–60% of women with recognized cardiac disease or hypertension were utilizing contraception, among those with diabetes mellitus fewer than 25% reported utilizing contraception. Clearly, if a reduction in diabetes-associated fetal malformations is to be achieved, active strategies to provide appropriate contraception during the preconceptional period must be developed and implemented.

THE IMPORTANCE OF POSTPARTUM CARE IN PRECONCEPTION CARE

It is important that women with gestational diabetes mellitus (GDM) come to understand whether they have overt, type 2 diabetes persisting after delivery of their babies so that their preconceptional glucose control can be optimized for the next pregnancy. Accordingly, ACOG and other expert bodies recommend testing of women with GDM in the postpartum period. Unfortunately, success in this area has fallen far short of expectations. In one study of postpartum GDM testing by Carson et al.[16] that summarized data from 13 studies involving over 10,000 GDM women, only 35% underwent postpartum testing for type 2 diabetes. When active outreach measures were utilized to improve compliance, only 65% of GDMs had been tested up to 12 weeks postpartum. Unfortunately, this leaves one-third to two-thirds of women at risk for type 2 diabetes undiscovered. In a subsequent pregnancy, such women frequently are not diagnosed before the end of the first trimester of the next pregnancy after organogenesis has taken place. Other studies have shown that in some populations, fewer than one-third of women ever attend their postpartum visit largely due to complicating social circumstances and lack of insurance funding.

UNDERUTILIZATION AND UNDERPERFORMANCE OF PRECONCEPTION CARE: WHAT CAN BE DONE?

Role of Health Insurance

A number of programs have been developed to incentivize healthcare providers to optimize identification and care of populations with chronic diseases ("Pay for Performance"). One example of this is the California P4P program overseen by the Integrated Healthcare Association, a consortium of eight health plans representing 10 million insured individuals.[17] The P4P Program focuses on seven elements encompassing cardiovascular, diabetes, musculoskeletal, prevention, respiratory, maternity, and utilization. P4P sets goals for quality care to be delivered by their providers and compensation bonuses are gauged to achieve improvement in specific health measures. In diabetes care, current elements for which practitioners and physician groups can qualify for additional funding include controlling HbA1c to a level below 8%, reducing low-density lipoproteins (LDL) into a healthy range and keeping blood pressure below 140/90 mmHg. The results from 2010 are at once encouraging and discouraging. Screening for LDL and glucose control was achieved in 90% of the physician groups but controlling HbA1c below 8% occurred in only slightly more than 50%. This obviously leaves approximately half of women at risk for pregnancy with HbA1c in a suboptimal range.

Although the results of the California P4P program among the insured population is encouraging, no similar programs are available to the uninsured or to many of those covered by Medicaid insurance. The National Institute for Reproductive Health documented that in 2004, 20% of U.S. women were uninsured (19 million).[18] Of these, half have had no regular doctor, 40% did not fill prescriptions due unaffordability, and 67% stated they need a care but could not get it due to cost. Figure 29-1, which demonstrates the numbers of uninsured women in reproductive ages trended from 2000 to 2010, shows an increase of six million uninsured women in the past decade.[19]

Fortunately, recent U.S. federal law requires that states participating in Medicaid extend Medicaid eligibility to all pregnant women with incomes below 133% of the federal poverty level (FPL).[20] However, no similar provisions exist for nonpregnant women, with Medicaid income eligibility thresholds as low as 19% in Alabama. While women who become pregnant, United States have uniform access to maternity care from the earliest diagnosis of pregnancy, preconception care remains unavailable to a substantial number of women with diabetes.

The Affordable Care Act (ACA) may indeed improve the picture of preconception care. For those states opting to participate in the Medicaid expansion, nonpregnant women with income below 133% of FPL will gain access to coverage. Through the new ACA insurance exchanges, a vast formerly uninsured population of nonpregnant women will have access to prenatal and preconceptional care regardless of their history and preexisting conditions. Unfortunately, at the time of this writing, a substantial number of states legislatures have declined to participate in the Medicaid expansion clause, leaving women in those states in a situation where they do not have ready access to preconception care.

PRECONCEPTION CARE: A WAY FORWARD

There are a number of seemingly insurmountable obstacles in the way of improving the picture for women with diabetes and at risk for diabetes when they are nonpregnant. Expanding insurance coverage for the nonpregnant population is on the horizon but will require participation of the remaining states presently resisting Medicaid expansion. Lack of prepregnancy planning on the part of women with or at risk for diabetes, and especially those with type 2 diabetes and obesity can be expected to be substantially suboptimal for the foreseeable future. Active outreach programs to at-risk women will be necessary and at present have not been put forward in an organized way by expert bodies such as ADA and ACOG.

What is potentially achievable and could represent significant progress is a wider availability of multidisciplinary clinics for women with diabetes. Multidisciplinary care means that realistic but encouraging advice regarding prepregnancy management and glycemic control is provided. There is little doubt based on

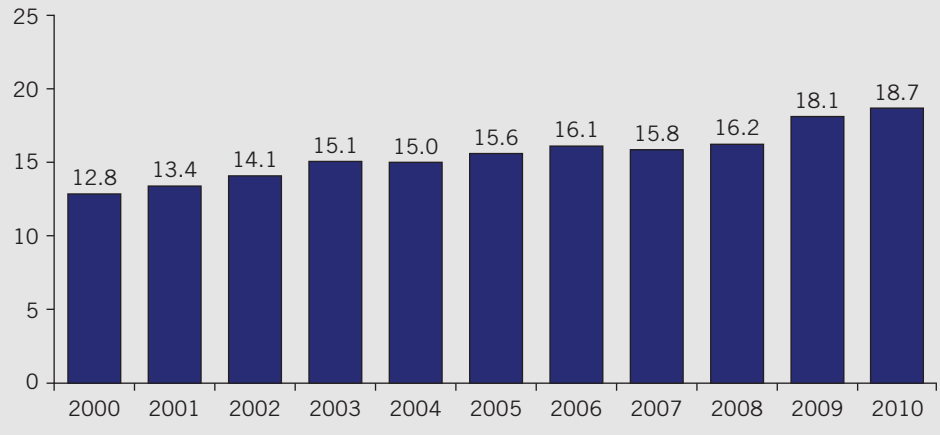

FIGURE 29-1 Millions of U.S. Women ages 19–64. (From Analysis of the March 2001–2010.[19])

the CEMACH study that the presence of an obstetrician, midwife, or other obstetrical care giver is an essential component of effective preconception care for women with diabetes.

It is also possible to improve postpartum visit compliance, incorporate effective lifestyle education and ensure glucose tolerance testing is performed for those with gestational diabetes and women who are obese. Moreover, expert bodies and insurance plans must emphasize these important aspects of obstetrical care, at least as important as successful delivery of the fetus.

Redesigning care models to promote effective and reliable handoff from obstetrical provider to primary care provider and a Medical Home that will treat all reproductive aged women as potentially preconceptional is essential.

Finally, utilization of effective contraception for all women with obesity and glucose intolerance is necessary if preconceptional glycemic targets are to be achieved and fetal status optimized. Contraception counseling must be actively incorporated into postpartum and routine care of all reproductive aged women if the presently excessive and correctable incidence of fetal anomalies is to be reduced.

Table 29-2 summarizes the desirable elements of a preconception care program for women at risk of diabetes.[21]

TABLE 29-2 Build a Preconception Care Program

Establish a multidisciplinary team
Regularly include CDE, dietician, physician, and obstetrical provider
Provide contraception
Set targets for conception: HbA1c, BP, BMI
Educate patient and family regarding pregnancy risks
Include maternal, fetal, and child outcomes
Prescribe folic acid
1–4 mg daily from at least 3 months before intended conception
Stop or control substance use
Assess over the counter medications and supplements
Assess, modify or discontinue medications with fetal risk
ACE, ARB, psychiatric
Evaluate and manage vascular complications
Ophthalmic
Renal
Cardiovascular
Thyroid
Optimize glucose Control
Use glucose targets and medications as for pregnancy
Achieve HbA1c < 6.5 before conception
Provide infertility consultation when appropriate

Source: Modified from Temple and Murphy.[21]

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Epidemiology and Prenatal Diagnosis of Congenital Malformations in Diabetic Embryopathy

30

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Practice doesn't make perfect
Practice reduces imperfection

Key Points

- Pregestational diabetes is a risk factor for birth defects and perinatal mortality.
- With rapid growth of the diabetic population, the number of the infants born with birth defects is projected to increase.
- Maternal glycemic control and adequate perinatal care can reduce the infant mortality rate. However, the rate of birth defects in infants of women with diabetes remains higher than that in the general population.
- The poor outcome of diabetic pregnancies in developing countries may be due to inadequate clinical care rather than racial background.
- Ultrasound is a reliable and commonly used diagnostic tool for detection of fetal abnormalities in diabetic pregnancies. Molecular biomarkers can be used as supplementary indicators in diagnosis.

INTRODUCTION

Although diabetes mellitus dates back to the beginning of humanity, encompassing centuries and various civilizations, the association between maternal diabetes and birth defects and perinatal mortality was not determined until the late 19th century.[1,2] Aggressive glycemic control and intensive perinatal care of pregnant women with diabetes have dramatically reduced the rate of fetal mortality. However, the rate of birth defects remains as high as 10%.[3–5] Making matters worse, the incidence of diabetes among women of childbearing age has increased over the past four decades, with no signs of leveling off or declining.[6] According to the recent report by the Centers for Disease Control and Prevention, nearly 26 million individuals at 20 years of age or older were diagnosed having diabetes in the United States, including 13 million women.[7] These data suggest that approximately 8000 babies will be born each year in the United States with maternal diabetes-associated congenital malformations.[4] Moreover, rapid increases in the number of diabetic individuals in developing countries have become a global concern in public health.[8,9]

Diabetes mellitus in pregnant women can occur prior to or during gestation. The former is referred to as pregestational (or preexisting) diabetes mellitus.[10,11] The latter is known as gestational diabetes, which may be a direct consequence of the altered maternal metabolism due to the changing hormonal milieu.[12,13] Pregestational diabetes can affect embryos at early developmental stages, and, thus, is more likely to result in higher perinatal mortality and structural malformation rates (Table 30-1).[10,14,15] It is estimated that the frequency of pregestational diabetes complicating pregnancies in the United States is 2%–5%.[16,17] Gestational diabetes, on the other hand, often is associated with newborn macrosomia and preterm birth (Table 30-1).[12] The incidence of gestational diabetes in the United States is nearly 5% of all pregnancies.[16,17]

Under maternal hyperglycemic conditions, embryos and fetuses are exposed to highly stressful environments generated by abnormal maternal metabolism. Although increased ketone bodies[18] and triglycerides[19] have been found to be associated with embryonic malformations, a strong correlation between hyperglycemia and high rates of birth defects has been demonstrated.[20–22] It is generally believed that hyperglycemia is the major teratogenic factor for birth defects. Therefore, early detection of diabetes in pregnant women is important for reducing fetal complications. In clinics, the level of glycosylated hemoglobin A (HbA1c), which is expressed

TABLE 30-1 Fetal Malformations in Diabetic Pregnancy

Gestation Stage	Abnormality
Preimplantation	
	Cell death
	Failure in implantation
First trimester	
	Severe structural malformations
	Growth retardation
	Early spontaneous abortion
Second trimester	
	Mild structural malformations
	Growth retardation
	Polyhydramnios
	Erythremia
	Spontaneous abortion
Third trimester	
	Macrosomia
	Respiratory stress
	Intrauterine demise

as percentage of total hemoglobin A, is used as an integrated retrospective index of glycemic status in pregnant women.[23,24] The introduction of HbA1c has permitted investigators to monitor and confirm the presence of hyperglycemia during very early stages of gestation.[24,25] The oral glucose tolerance test also is useful for screening gestational diabetic status in the population.[24,25]

EPIDEMIOLOGY

Prior to widespread use of insulin to manage pregnant women's glucose levels, the maternal diabetes-associated perinatal mortality rate was as high as 70%, and maternal mortality reached 30%–40%.[26,27] After the introduction of insulin, maternal mortality decreased dramatically, while perinatal mortality reduced slowly and has reached the current rate of 4%–13%.[28–34] The decline of maternal and perinatal mortality is believed to be the result of insulin administration along with clinical care and aggressive perinatal and neonatal management.[20,29,35–37] Unfortunately, the rate of developmental defects has not changed, and the reasons for this are still not completely understood.

During the past decades, efforts have been made to investigate the epidemiology of birth defects of infants of diabetic mothers in developed and developing counties around the globe. In Europe, a number of studies conducted in the early 20th century have shown that birth defect rates in infants of diabetic mothers were 10%–18%. The studies show declines in fetal malformation rate to 8%–9%, and include a number of large scale surveys by the Academic Hospital Groningen and Isala Clinics of the Netherlands,[38] a German group,[39] groups in Great Briton,[40,41] the Gestation and Diabetes in France Study Group,[42] the Spanish Collaborative Study of Congenital Malformations,[43,44] and the Centers for Disease Control and Prevention.[45]

Retrospective examinations of clinical records in Australia and New Zealand show higher perinatal mortality rates in the offspring born to mothers with preexisting diabetes mellitus (5.4%–7.5%) than that of infants born to women with gestational diabetes (1.4%–1.6%).[46–48] It is noted that the perinatal mortality declined to 3.9% after the 1980s, due to successful control of hyperglycemia in the women. However, the prevalence of congenital malformations has remained as high as 9%–13%.[46–48]

In North America, perinatal mortality rate and fetal malformation rate were also as high as 17% in the early 20th century,[31,45,49,50] but declined markedly to 6%–7% by the latter half of the 20th century, according to large scale epidemiological studies, including the U.S. Centers for Disease Control and Prevention Study (1940–1988),[45] Atlanta Birth Defects Case-Control Study (1968–1980),[51] Baltimore-Washington Infant Study,[52] Parkland Hospital Study in Dallas, Texas (1991–2000),[53] and National Birth Defects Prevention Study (1997–2003).[5]

In Africa and Asia, available data have shown various types of adverse outcomes of diabetic pregnancies with high perinatal mortality of up to 12%–20% in the last century.[54–63] Because many deliveries take place in nonclinical settings where no medical records are kept, it is impossible to obtain reliable birth defect rates from some countries. However, a study conducted in Singapore, one of the developed Asian countries, reported a 15.5% malformation rate in infants of diabetic mothers.[64]

The poorer outcomes of diabetic pregnancies in developing countries may be due to reduced availability and substandard quality of perinatal care.[64] Whether there also is an underlying difference in the prevalence of diabetes among racial/ethnic groups in these countries is still not clear. A number of reports have shown a high prevalence of diabetes and poor pregnancy outcomes in Asian and African women, compared with Caucasian women, even in the developed countries.[65–69] However, other studies found no difference in pregnancy outcomes between Caucasian and Indo-Asian women.[70]

MECHANISMS OF DIABETIC EMBRYOPATHY

Developmental malformations in infants of diabetic mothers exhibit a great diversity, ranging from congenital structural defects, to functional defects, to lower birth weight, to macrosomia.[14,30,71,72] Because maternal diabetes can adversely affect almost every aspect of embryonic development and maternal–fetal interaction, the frequency and severity of abnormalities appear to be correlated with the gestational stages at which the embryo or fetus begins to be exposed to hyperglycemia (Table 30-1).[73–75]The first trimester is the critical period of embryonic development, in which organ formation undergoes morphogenesis.[73,78] In the first trimester, maternal hyperglycemia can cause congenital anomalies, growth retardation, and spontaneous abortion.[20,76,77] In the second and third trimesters, maternal hyperglycemia usually leads to functional defects, fetal hyperinsulinemia, fetal respiratory stress, and fetal excessive growth.[74,75]

Structural abnormalities caused by maternal diabetes can occur in many organ systems. The mechanisms by which maternal hyperglycemia induces embryonic malformations have not been

fully understood. Studies using animal models have shown that hyperglycemia affects various cells and tissues in the embryo.[78–80] The extraembryonic tissue (yolk sac) plays an important role in early embryogenesis by transporting nutrients and exchanging gases.[81] The yolk sac functions as an early route of nutrition for the embryo, characterized by Reece et al. (Figure 30-1).[82] In diabetic embryopathy, the extraembryonic tissue's functions are severely impaired by maternal hyperglycemia, manifested by shorter microvilli, swollen mitochondria, reduced number of rough endoplasmic reticulum (ER), and lipid droplets in the endothelial cells.[83,84]

The most common and severe abnormalities in diabetic embryopathy are seen in the central nervous and cardiovascular systems (CNS and CVS).[5,71] The development of the CNS begins with formation of the neural tube, a process known as neurulation. On the dorsal region of the embryo, the neural plates differentiate from the ectoderm and develop dorsal-laterally into the neural folds.[85,86] The neural folds further grow, bend, and eventually fuse at the midline along the anterior–posterior body axis to form the neural tube (Figure 30-2).[87] Most of the anomalies in the CNS result from abnormal development of the embryonic neural tube and are known as neural tube defects (NTDs).[11,12,14]

Abnormalities in the CVS are associated with aberrant development of various processes, including cardiac chamber formation, myocardial development, cardiac septation, and valve formation.[88–91] Cardiac septal defects are the most common heart abnormalities in diabetic embryopathy, and are associated with the endocardial cushions in the atrioventricular junction and outflow tract. The endocardial cushions are bulbous structures composed of an endocardial (endothelial) cell layer and acellular cardiac jelly within the heart tube.[92] The endocardial cells differentiate into mesenchymal cells, a process referred to as epithelial–mesenchymal transformation, and migrate into the cardiac jelly to promote the endocardial cushions growing toward each other and eventually fusing together to form continuous septa (Figure 30-3).[92,93]

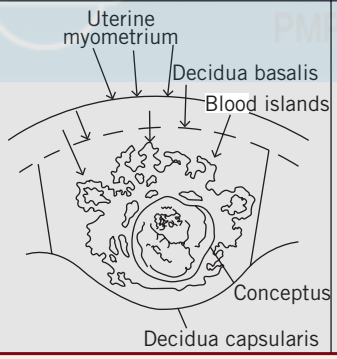
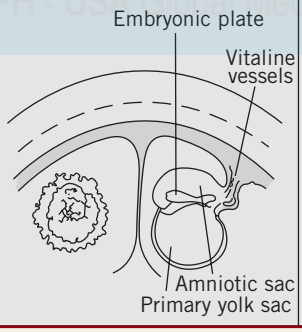
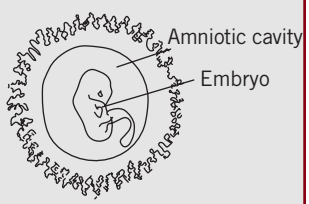
Type of nutrition	Histotrophic nutrition	Hemotrophic nutrition	Placental nutrition
Stage of development	Pre-yolk sac	Yolk sac	Placenta
Gestational age	<2 weeks	2–5 weeks	>5 weeks
Schematic representation			

Figure 30-1 Schematic illustration of yolk sac development. (Adapted from Reece, et al.[125])

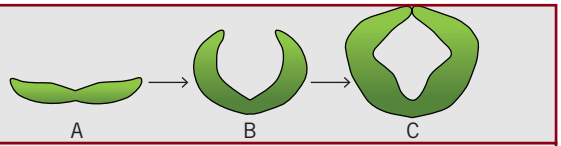


Figure 30-2 Schematic illustration of neurulation. A, Neural plate. B, Neural fold. C, Neural tube.

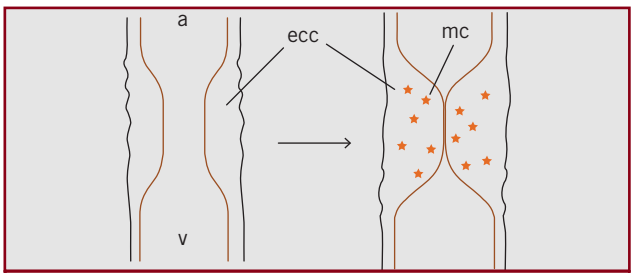


Figure 30-3 Schematic illustration of endocardial cushion development. a, atrium; ecc, endocardial cushion; mc, mesenchymal cell; v, ventricle.

Associated with the dysmorphogenesis of the embryonic structures, programmed cell death (apoptosis) and cell proliferation (mitosis) are increased and decreased, respectively.[79,80,88,90,94] Cell migration, another important cellular activity in organogenesis, has also been shown to be suppressed by maternal hyperglycemia. This includes the migration of neural crest cells that contribute the development of the craniofacial structures and outflow segment of the heart,[95–97] and the migration of endocardial cells, which is required for the development of the endocardial cushions and cardiac septation.[89,98]

The aberrant cellular activities seen in diabetic embryopathy are the consequences of disrupted intracellular signaling. Under hyperglycemic conditions, glucose influx into the embryonic cells perturbs normal glucose metabolism, producing metabolites that change intracellular conditions and modify proteins, such as glycosylation, to alter their activity.[94,99] These abnormal intracellular changes have a profound impact on expression of genes that encode proteins which control cellular activity and embryonic morphogenesis.[100,101]

Maternal diabetes alters the molecular activities in embryonic cells. Although some of the molecular pathways and intermediates have been widely studied, while others have yet to be confirmed, Figure 30-4 depicts a very plausible hypothetical model of the underlying etiological mechanisms of diabetes-induced birth defects. Maternal hyperglycemia stimulates the expression of inducible nitric oxide (NO) synthase (iNOS), the only member of the NOS family (iNOS, neuronal NOS, and endothelial NOS) that sensitively responds to environmental stimulations.[102] Upregulation of iNOS leads to overproduction of NO, which alters protein activity via cysteine nitrosylation and tyrosine nitration, generating so-called nitrosative stress.[103,104]

Hyperglycemia disturbs the function of organelles such as the ER and mitochondria.[105,106] Dysfunction of the ER compromises the folding and processing of newly synthesized polypeptides, causing retention of proteins in the ER lumen and resultant ER stress.[107] Under stress conditions, cells activate a number of molecular signaling pathways, known collectively as the unfolded protein response (UPR), which express chaperone proteins to resolve the protein folding crisis, modify proteins to block translation, inhibit cell division, and trigger apoptosis to eliminate the abnormal cells.[108] Hyperglycemia also disrupts the functions of mitochondria, including the generation of adenosine triphosphate via the electron transfer chain.[109] Disruption of electron transfer generates high levels of reactive oxygen species (ROS).[110] With the depletion of endogenous antioxidants and downregulation of antioxidative enzymes, such as superoxide dismutases, the imbalance of ROS levels and antioxidative buffering generates oxidative stress (Figure 30-4).[111] Interaction between these two pathways remains to be delineated.

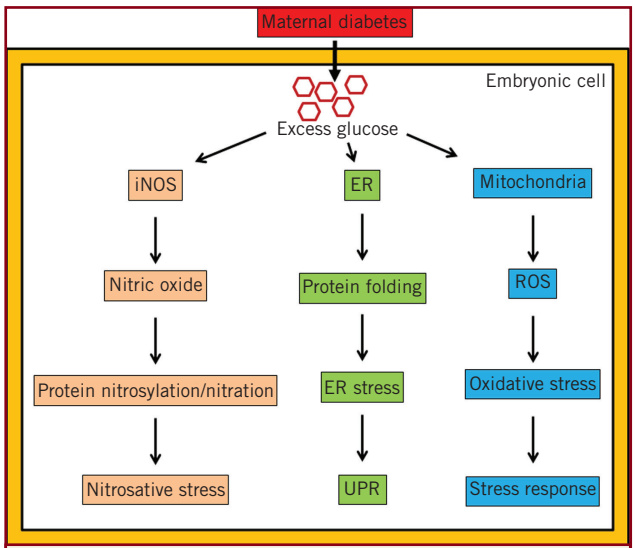


Figure 30-4 Schematic illustration of hypothetical metabolic changes in the embryonic cell under hyperglycemic conditions.

Oxidative and ER stress alter gene expression, protein activity, and intracellular signal transduction, leading to inhibited cell mitosis and promoted apoptosis. Studies in animal models of diabetic pregnancies have revealed that members of the protein kinase C and mitogen-activated protein kinase families are involved in hyperglycemia-induced apoptosis.[79,112] These kinases regulate apoptotic factors in the Bcl-2 and caspase families, which have been shown to play a role in diabetic embryopathy.[113,114]

Understanding the mechanisms underlying embryonic malformations in diabetic pregnancies sheds light on the development of effective interventions to prevent birth defects in infants of diabetic mothers. For example, oral treatment with an iNOS inhibitor can decrease NTD rate in the embryos of diabetic animals.[115] Treatments with antioxidants, such as vitamins E and C, *N*-acetylcysteine, and lipoic acid, can reduce NTD rates in animal models and in animal embryos cultured in high concentrations of glucose.[79,112] It is highly conceivable that, with further basic research to understand the mechanisms of diabetic embryopathy, effective interventions will be developed to protect embryos from maternal hyperglycemic insult within the near term.

ANOMALIES AND DIAGNOSIS

Fetal Growth

Lower birth weight, premature birth, and gross hypoplasia (such as caudal regression) are frequently seen in the newborn infants of mothers with pregestational diabetes.[116] Macrosomia is often associated with gestational diabetes mellitus.[117,118] Ultrasound has been widely used to monitor fetal development and detect structural abnormalities,[119] and is proven to be an important approach in diagnosing maternal diabetes-associated fetal anomalies and assessing fetal growth.[120–122]

Because fetal growth is one of the most common developmental aspects affected by maternal diabetes mellitus, early detection of abnormal growth benefits the birth outcomes of diabetic pregnancies. Measuring the crown-rump length, the long axis of the embryo, is the most accurate method of fetal growth assessment and estimating gestational age in the early period of pregnancy.[123,124] However, after 12 weeks of gestation, this measurement becomes less accurate because of variable degrees of fetal flexion.[125] In the second trimester, measurements of the biparietal diameter (BPD) are reasonably accurate (±7–10 days) for gestational age estimate.[125–127] In addition to the BPD the occipitofrontal diameter, the distance from the mid echogenic plane of the occipital bone to the mid echogenic plane of the frontal bone, should also be measured.[128,129] By knowing the biparietal and occipitofrontal diameters, the head circumference can be calculated.[128,129]

Other fetal growth measurements include transverse cerebellar diameter (TCD), abdominal circumference (AC), and fetal long bones. The TCD has been used to evaluate the growth of the fetal head and body.[128–130] Because the posterior fossa is not affected by external pressure, the measurements of TCD are independent of the fetal head and provide more precise and accurate information about fetal growth than other measurements of the fetal head.[128–130]

The AC can be used to predict birth weight and fetal growth in diabetic pregnancy.[131,132] Because the fetal liver is the organ most affected by maternal diabetes, the level of the fetal liver should be chosen as the plane for the AC measurement. Gestational age and fetal growth can also be estimated from the measurements of the fetal long bones such as the femur, humerus, tibia, and ulba.[122,133,134]

Macrosomia is the most frequent phenotype of gestational diabetes, ranging from 20%–32%. It is defined as a fetal weight in excess of 4000 g or a birth weight above the 90th percentile for gestational age.[135,136] Prenatal diagnosis of macrosomia utilizes BPD versus AC, and head versus chest dimensions.[118,120]

Central Nervous System

The most common fetal abnormalities in diabetic embryopathy are present in the CNS (Table 30-2).[14,71,78,80] These malformations can be reproduced in diabetic rodent models, allowing experimentation to delineate the underlying mechanisms (Figure 30-5).[79,80,94,112]

TABLE 30-2 Major NTDs in Diabetic Embryopathy

Region	Defect
Brain	Anencephaly Excencephaly Arhinencephaly Holoprosencephaly Microcephaly
Spinal cord	Spina bifida

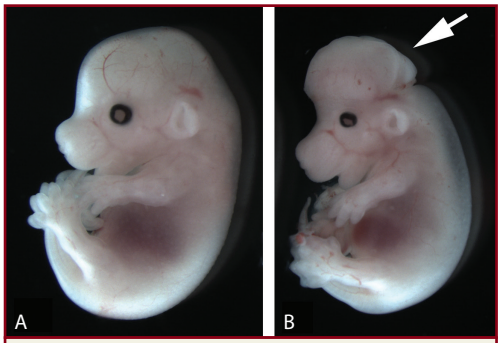


Figure 30-5 NTDs in fetuses (13 days of gestation) of diabetic mice. A, Nondiabetic control. B, Diabetes. Arrow indicates exencephaly.

Anencephaly

Anencephaly is an anomaly in the forebrain, which occurs when the neural tube fails to close completely at the cranial pole during fusion of the neural folds.[137,138] The cerebral hemispheres are usually absent, whereas the brain stem and portions of the midbrain are present (Figure 30-6). In association with this forebrain defect, the cranial vault is absent, although portions of cranial bones may be present.[137,139] Fetuses with anencephaly also can have spina bifida, cleft lip or palate, clubfoot, omphalocele, and polyhydramnios.[137–139] Prenatal diagnosis of anencephaly is possible in the first trimester, but is usually not obvious until 12 weeks of gestation. The phenotype can be recognized when the fetal brain appears flat in ultrasound images.[125,140] In the second trimester, anencephaly can be recognized by the poorly formed cranial bones and the symmetric absence of the calvarium.[125,137,140]

Holoprosencephaly

Holoprosencephaly is a relatively rare group of brain defects. It is the result of incomplete separation of the cerebral hemispheres.[141] Based on the degree of hemispheric nonseparation, holoprosencephaly is categorized into alobar, semilobar, and lobar types, with alobar being the most severe malformation.[141,142]

Holoprosencephaly can be diagnosed as early as 14 weeks' gestation, although diagnosis at the 20th week anomaly scan is more common.[143–145] Alobar and semilobar holoprosencephaly can be detected by the complete or partial absence of the midline echo within the fetal head.[144,146] Because of the defect in cleavage of the two hemispheres, the anterior cerebral artery runs along the internal side of the frontal bone. The sign of a "snake under the skull" in the sagittal view of the brain in a sonograph is commonly used as a marker for all the three types of holoprosencephaly.[146,147]

Microcephaly

When the head circumference of the fetus is below the third to fifth percentile, the fetus can be considered as having a microcephalic defect.[148] However, this standard does not apply to all children falling in this range because a number of factors can contribute to smaller brain sizes in fetuses who may be normal such as intrauterine growth

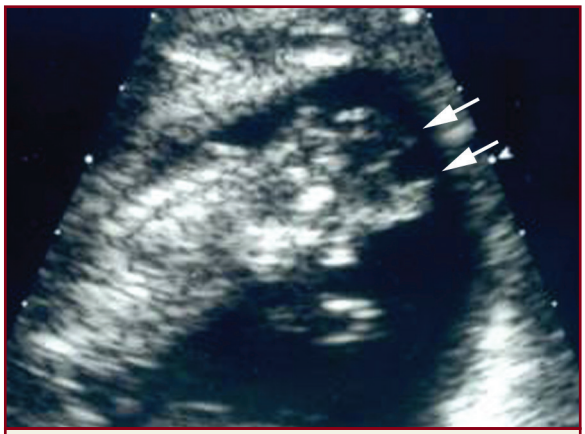


Figure 30-6 Ultrasonic detection of a NTD in a human fetus at week 12 of gestation. Arrows indicate anencephaly.

restriction and irregular growth during gestation.[140] In severe cases of irregular growth, the head circumference can be more than three standard deviations less than the mean.[140] The diagnosis can be suspected *in utero* when the BPD is discrepant by more than five weeks from the menstrual dates.[128] It is necessary to measure the head circumference in relation to other biometric parameters such as fetal bone length and head/body ratio. Because microcephaly is difficult to definitively diagnose using ultrasound, magnetic resonance imaging may be used to confirm this condition.[140]

Spina Bifida

Spina bifida, characterized as a failure in neural tube closure in the dorsal midline, occurs at a high frequency among fetuses of women with diabetes.[31,137] In the coronal plane, the fetal spinal column appears as three parallel lines, with the central line representing the vertebrae.[149–151] In the transverse plane, the neural canal appears as a closed circle. In many cases of spina bifida, there is "splaying" of the laminae, which creates a picture of a V-shaped spinal configuration on transverse scan or of a longitudinal scan in the area of the defect. A detailed diagnosis of the spine can prove a formidable task when the fetus is very active or in a less than suitable position.[150,152]

Peripheral Nervous System

Maternal diabetes also affects the development of the peripheral nervous system.[80,153] For example, the cranial ganglia fail to fully develop in fetuses of diabetic animals.[95,154] This may be due to impaired migration of the neural crest cells,[153,155] which are vulnerable to hyperglycemic insult.[95,155]

Functional Abnormalities

Functional defects in the infants of diabetic mothers have been described and are correlated with the abnormal development of the nervous systems. Defects include marked delay of *in utero* movement of fetuses, compared with nondiabetic pregnancies.[156] Children of diabetic mothers can have abnormal patterns in movement and sleep cycle, as well as memory deficiencies.[157–159] A wide spectrum of neurologic and psychological defects, including cerebral handicap, mental retardation, reading disability, speech disturbance, behavior disturbance, psychosis, and deafness, have been found to be associated with maternal diabetes mellitus.[160–162] Some of these problems may be caused by birth trauma because infant macrosomia and shoulder dystocia can lead to damage to the head and neck or hypoxic necrosis.[163,164] Nevertheless, a strong correlation has been established between some of these defects and maternal hyperglycemic insults to the fetuses.

Cardiovascular System

Cardiovascular defects in fetuses of diabetic mothers are present in all the cardiac structures, including the atria, ventricles, septa, outflow tracts, and valves (Table 30-3).[5,71,72,116] Most of the abnormalities have been recapitulated in animal models (Figure 30-7).[88,97,153,165]

Formation of the cardiac defects largely occurs in embryos exposed to hyperglycemia in the early first trimester (>7 weeks of gestation),[73] which has also been demonstrated experimentally in an animal model.[89] When hyperglycemia occurs during the late gestational period, after the cardiovascular structures have formed, there is an increased risk of myocardial hypertrophy.[166] The myocardial hypertrophy seen in the infants of diabetic mothers includes larger heart, thickened myocardium, thickened interventricular wall, and asymmetric hypertrophic valves.[167,168]

In a normal fetal heart, left ventricular fractional and circumferential shortening is greater than that of the right ventricle. However, the fetuses of diabetic mothers with hypertrophic heart have decreased biventricular myocardial fractional shortening, smaller left ventricular stroke volume, and diminished left ventricular output (Figure 30-8).[169,170] The hypertrophic phenotype is believed to be a result of fetal hyperinsulinemia.[171]

Because abnormalities of the cardiovascular system involve structural and functional defects, fetal echocardiography is the primary diagnostic tool used to assess fetal cardiac structure.[172,173] With this technology, accurate assessment of cardiovascular structure can be obtained with two-dimensional real-time analysis. Pulse-time and continuous-wave Doppler can be used to evaluate intra- and extracardiac flow qualitatively and quantitatively. A complete fetal echocardiographic examination should incorporate the following standard views: (1) the four-chamber view; (2) the left ventricular long-axis view, with visualization of the aortic outflow tract; (3) the short-axis view, with visualization the

TABLE 30-3 Major CVS Defects in Diabetic Embryopathy

Cardiac Structure	Defect
Ventricles	Hypoplastic left heart Hypoplastic right heart
Septa	Atrial septal defects Ventricular septal defects Atrioventricular septal defects
Outflow tracts	Transposition of the great arteries Double-outlet right ventricle Coarctation of the aorta Aortic stenosis Truncus arteriosus
Valves	Pulmonic valve atresia Pulmonary valve stenosis
Complex defects	Tetralogy of Fallot

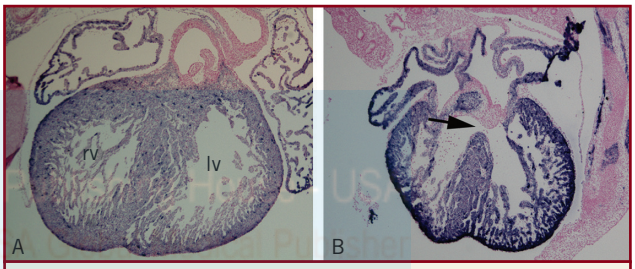


Figure 30-7 Cardiac defects in fetuses (15 days of gestation) of diabetic mice. A, Nondiabetic control. B, Diabetes. Arrow indicates ventricular septal defect. lv, left ventricle; rv, right ventricle.

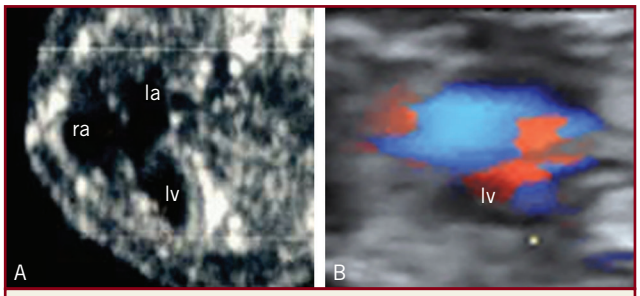


Figure 30-8 Hypoplastic left ventricle in human fetal hearts at week 12 of gestation. A, Sonograph. B, Color Doppler. la, left atrium; lv, left ventricle; ra, right atrium.

pulmonary outflow tract and ductus arteriosus; and (4) the longitudinal view of the aortic arch. These views will provide details of the intracardiac anatomy and evaluation of the conotruncus and left ventricular outflow tract. The scan should also include an evaluation of the relationship of the great arteries to one another. A normal crossing relationship virtually excludes the possibility of transposition of the great arteries.[125]

The echocardiographic features of the fetus with diabetic hypertrophic cardiomyopathy include restricted ventricular filling, dynamic left or right ventricular outflow tract obstruction, and global myocardial hypertrophy. Some of or all these findings may be present in any individual fetus and to varying degrees.[168,174] M-mode and real-time two-dimensional echocardiography can be used to measure the ventricular septum. The normal thickness of the septum should be less than 6 mm during the third trimester.[175] The measurements should be taken just below the atrioventricular valves from the long-axis view of the left ventricle. During systole, the anterior leaflet of the mitral valve may be seen to be closely opposed to the interventricular septum, a phenomenon known as systolic anterior motion.

Color flow Doppler mapping, which can assess functional stenosis or dynamic obstruction, has been utilized in combination with the fetal echocardiography to make more accurate diagnoses of cardiac anomalies. For example, when applied to a two-dimensional image or M-mode image, color flow Doppler mapping can precisely detect the point in the cardiac cycle when turbulence begins. Pulse-wave Doppler is used to examine ventricular inflow patterns in the fetuses that have evident hypertrophic or hypoplastic cardiomyopathy (Figure 30-8). Left ventricular outflow tract obstruction and conotruncal abnormalities are commonly seen in fetuses of diabetic mothers. Assessment of these abnormalities can be made with both pulse-wave and directed continuous-wave Doppler techniques.[125]

CRANIOFACIAL REGIONS

In the craniofacial regions, the most common anomaly is hemifacial microsomia and microtia in newborns of diabetic mothers.[176,177] Cleft palate/lip also occurs in relatively high frequency.[16,178] Hearing impairment in the children has been found to be associated with diabetic pregnancy.[176,177,179] Some of the cases are likely due to the defects in the inner and middle ears.[179] It has been observed that maternal hyperglycemia alters the development of the Meckel's cartilage, which gives rise to the auditory bones in the middle ear.[153]

The growth of the head of the fetus is an indication of potential microtia. Measurement of the size of the head using two-dimensional and three-dimensional ultrasound have been applied to diagnose hemifacial microsomia and microtia.[180,181] More precise measurements of the forehead length, forehead height, and forehead area can be obtained by drawing a line from the apex of the philtrum to the nasion across the anterior forehead.[181] These data are used to calculate the forehead index. Diagnosis of these craniofacial anomalies is achieved by comparing the forehead index of the subject with that of normal fetuses at the same gestation stage.[181]

To diagnose cleft lip or cleft palate, a combination of coronal and axial scans using two-dimensional ultrasound is commonly used. Cleft lip can be easily recognized from coronal scan images. In cases where cleft lip extends into the palate, the axial scan of the maxilla can provide the image of the defects.[180] The cases of lateral cleft lip/palate often present so-called maxillary pseudomass visualized in two-dimensional sonographs.[182]

SKELETAL SYSTEM

The skeletal anomalies that most frequently occur in the infants of diabetic mothers include sacral agenesis and hypoplasia, hypoplastic limbs, and pes equinovarus.[30,71,72,183] Hallucal polydactyly is also seen in the newborns of diabetic mothers.[184] Fused cervical vertebrae and agenesis of ribs has also been reported in humans and animal models.[177]

GASTROINTESTINAL ABNORMALITIES

The most common gastrointestinal anomalies in the fetuses of diabetic mothers are small bowel atresia, left colon syndrome, and imperforate anus.[185] Duodenal atresia is a common form of small bowel obstruction and can be diagnosed by sonography. Sonographic findings in small bowel atresia are characterized by dilated sonolucent "masses" that occupy the fetal abdominal cavity. The "double-bubble" phenomenon in duodenal atresia can be seen in jejunal atresia.[186] Because the double-bubble picture is not always present before 24 weeks' gestation, ultrasound examination may result in false-negative diagnoses in the second trimester. Therefore, it is necessary to perform ultrasound diagnosis during the third trimester. Determination of disaccharidase activity in the amniotic fluid before the 22nd week of gestation also can be helpful in making the diagnosis.[186] Colonic atresia can be detected as enlarged echo-free colonic loops in the lower abdomen with active peristalsis. Polyhydramnios is less frequent than with proximal lesions.[187]

GENITOURINARY ABNORMALITIES

Structural defects in the genitourinary system are seen frequently in the newborn infants of diabetic mothers.[31,73,188] The malformations include renal agenesis, uterine agenesis, ureteral duplication, hydronephrosis, renal cysts, oligohydramare, hypoplastic vagina, hypoplastic testes, and ambiguous genitals.[15,31,188] These anomalies are occasionally associated with caudal regression syndrome, but more often occur independently.[15,189] Fetal kidneys can be observed in embryos around 12 weeks of gestation using high-resolution and high-frequency ultrasonography, making

diagnosis of renal agenesis and abnormalities possible from this stage.[125,190] In many cases, diminution in amniotic fluid occurs. The absence of the amniotic fluid "window" makes the visualization of kidneys very difficult. The problem can be even more complicated if the fetal adrenal undergoes hypertrophy, creating the phenomenon that a structure seems present in the area where the kidneys usually reside. Duplication of ureter can be detected as a cystic structure adjacent to the kidney.[125]

CAUDAL REGRESSION SYNDROME

Caudal regression syndrome, also known as caudal dysplasia, is characterized by the absence or hypoplasia of caudal structures.[183,191] It is a relatively rare condition that complicates 1 in 200 to 1 in 500 diabetic pregnancies. The anomaly may result from a defect in the mid posterior axis mesoderm of the embryo occurring before the fourth week postconception.[183,192] Caudal regression syndrome can be diagnosed by noting a shortened spine and abnormal lower limbs, and can be detected in the fetus as early as second trimester.

MOLECULAR MARKERS FOR DIAGNOSIS

Biomolecules in maternal circulation have been found to be associated with fetal abnormalities. These biomarkers include α-fetoprotein, human chorionic gonadotropin, maternal serum unconjugated estriol, and Inhibin-A.[125,193–195] Because mechanisms underlying the molecule-anomaly correlation are still not clear, biomarkers can only be used as supplementary indicators to ultrasound examinations. To increase the reliability of the molecular indication, multiple markers are usually used.[194,195] In addition to protein markers, maternal circulating noncoding RNAs have been explored as potential biomarkers for NTDs.[196] Further research is needed to validate the reliability of the RNA markers for future application in diagnosis.[197] Not only does the reliability of biomarkers in diagnosis need to be improved but also the sensitivity of biomarkers must be enhanced to achieve the goal of early diagnosis (ideally before eight weeks of gestation), as most biomarkers are only detectable in the second trimester.[194,198]

SUMMARY

Diabetes mellitus in early pregnancy increases the risk of birth defects in infants, as well as perinatal mortality. Although aggressive glycemic control and perinatal care have markedly reduced these complications, the birth defect rate in diabetic pregnancies (10%) remains much higher than that in the general population (3%). Hyperglycemia disturbs intracellular metabolic homeostasis to generate nitrosative, oxidative, and ER stress in the embryo, leading to decreases in cell proliferation, increases in programmed cell death, and, eventually, malformations. Fetal structural defects are seen in almost every organ system. Diagnosis of the abnormalities largely relies on sonography, with molecular biomarkers as supplementary references; however, early detection of fetal anomalies (<10 weeks) is still a challenge.

Diabetic embryopathy is a global public health issue. Although pregestational screening for maternal diabetes, perinatal care, and postnatal management are available for most pregnant women in developed countries, the rate of birth defects in infants of diabetic mothers remains high. With the prevalence of type 2 diabetes in the general population on the rise, especially among women of childbearing age, diagnosing and managing diabetic pregnancies pose significant challenges for the medical community. In developing countries the rates of birth defects and mortality are high because of unavailable and inadequate care for pregnant women, statistics which are compounded by an increasing prevalence of diabetes in these countries. Therefore, it is vital to develop effective interventional approaches to prevent embryonic malformations in diabetic pregnancies such as dietary multinutrients.

Modern technology provides powerful tools for an early diagnosis of fetal abnormalities at the morphological and molecular levels. However, because hyperglycemia insults on embryo occur at very early pregnancy, detection of diabetes in women prior to pregnancy is also crucial to achieve the goal of preventing birth defects in diabetic pregnancies. Screening for diabetes in childbearing age women and medical counseling before pregnancy should be essential components of perinatal care.

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Type 2 Diabetes in Pregnancy

A Growing Concern

31

Oded Langer, MD, PhD

The greatest barrier to discovery is not ignorance but the illusion of knowledge.

—David Boorstein

Key Points

- Gestational diabetes mellitus (GDM) is considered an early stage in the natural history of type 2 diabetes; both share similar pathophysiology and phenotypic characteristics and can be considered the same disease with different names
- Women with type 2 diabetes may have few or no classic symptoms of hyperglycemia
- Of all cases of type 2 diabetes, 30%–50% are undiagnosed
- Risk factors for type 2 diabetes include previous GDM, obesity, advancing age, weight gain in adulthood, central fat distribution, ethnicity, family history of diabetes, low birth weight, sedentary lifestyle, impaired glucose, and fasting tolerance test
- Microvascular and macrovascular complications have similar rates in type 1 and type 2 diabetes
- Intensified treatment to achieve glycemic control reduces the risk of microvascular complications but the effect of strict glycemic control on the risk of macrovascular disease (especially in well-established type 2 diabetes) is less certain
- Psychosocial (e.g., motivation and capacity for self-care) and clinical factors (e.g., age, presence/absence of coexisting conditions, and presence/absence of hypoglycemia) need to be considered in setting target range for glycemic control
- Lifestyle modification and pharmacological therapy (especially insulin) are recommended initial therapies for most patients
- The treatment approach needs to address cost, side effects, and short and long-term safety

INTRODUCTION

There has historically been no major focus on type 2 diabetes and pregnancy despite the fact that there is a greater prevalence of type 2 than type 1 diabetes in the population. The numbers of persons with type 2 diabetes in the United States will be more than triple by 2050 from the current estimate of 26 million.[1] The increasing incidence of type 2 diabetes is largely attributable to lifestyle changes (diet and activity levels) that often lead to obesity. The problem is global, affects affluent and lower-income societies, and carries high societal costs. Commonly associated metabolic abnormalities include hypertension, dyslipidemia, inflammation, hypercoagulation, and endothelial cell dysfunction.[2–4]

Approximately 30%–50% of all people with type 2 diabetes may be undiagnosed. The subtle onset (sometimes 9–12 years) of the disease may contribute to the delay in diagnosis and, as a result, account for the presence of complications. Women at risk for diabetes are at similar risk for cardiovascular and peripheral vascular diseases leading to early death.[5,6] In contrast to the diligence and extraordinary efforts to maximize quality of life for both pregnant and nonpregnant type 1 diabetic women, a comparable endeavor has not been generated for those with type 2 diabetes. Type 2 diabetes is the leading cause of blindness, nontraumatic lower-limb amputation, and chronic kidney disease in the United States.[7]

The historic negligence in the treatment and management of type 2 diabetes in pregnancy has several explanations. Traditionally, noninsulin-dependent diabetes mellitus (NIDDM) was considered adult-onset diabetes often diagnosed subsequent to a woman's reproductive life. It has been demonstrated that type 2 diabetes, although more frequent in the second half of life, now occurs earlier. Over the past 10 years, more women of childbearing age, adolescents, and even children have developed type 2 diabetes.[8] WHO data from 1992 showed the prevalence of diabetes in women of childbearing age (20–39 years) to be highest among Native Americans, Micronesians, rural Fijians, and aboriginal Australians all of whom have very high population rates of type 2 diabetes.[9] In adolescents, type 2 diabetes has been increasingly noted in native Canadian and American populations, Mexican–Americans, African–Americans, and Japanese.[10] The rise in the prevalence of type 2 diabetes in general, and in younger people in particular, has led to an increasing number of women with type 2 diabetes in pregnancy. Furthermore, it is well recognized

that approximately 10% of gestational diabetic women are, in fact, type 2 diabetics.[11] The current obesity epidemic, associated with an increased prevalence of type 2 and gestational diabetes, has further aggravated this phenomenon.

The traditional linear lifestyle has been usurped by a cyclical lifestyle in which people postpone marriage, marry, and divorce more frequently, delay childbearing, and so forth; it has unmasked a cohort of women with a preponderance of type 2 diabetes. A study of diabetes prevalence in the United States found that, whereas the prevalence of diabetes increased by 33% overall from 1990 to 1998, the prevalence in individuals aged 30–39 years increased by 70%.[12] Furthermore, in vitro fertilization of older women has pushed the envelope of first time or older motherhood beyond the traditional term and has created an entirely new set of obstetric criteria for the physician to ponder.[13] Therefore, the past decade has seen the emergence of type 2 diabetes in pregnancy with its attending negative implications. Current research indicates that we may be underestimating the true prevalence of type 2 diabetes in pregnancy, and that the adverse maternal and fetal outcomes in previously threatening type 1 diabetic pregnant patients are now as significant in type 2 diabetic women.

RISK FACTORS FOR THE DEVELOPMENT OF TYPE 2 DIABETES

A discussion of gestational diabetes necessitates a review of the pathophysiology of type 2 diabetes as they are similar. Type 2 diabetes occurs in 3%–5% of the U.S. population and affects over 10 million individuals.[14] In Mexican–American and other ethnic groups, the prevalence of the disease is much higher, 15%–20%, and in females over age 50 it exceeds 30%. Moreover, the age of onset of type 2 diabetes in Mexican–Americans is younger,[15,16] and the risk and severity of microvascular complications has increased.[17–20] As observed in Caucasians, the risk of macrovascular complications in Mexican–Americans with type 2 diabetes has also increased.[21,22] Both Caucasian and Mexican–Americans have an increased prevalence of dyslipidemia[23,24] and hypertension[25–28] that represent major cardiovascular risk factors. Moreover, these factors have an additive effect to cause coronary artery disease and stroke. Results from the Diabetes Control and Complications Trial (DCCT) study, as well as from other smaller studies,[29–31] have clearly established hyperglycemia as a major risk factor for microvascular and, perhaps, macrovascular complications.

Consequently, great emphasis has been placed on tight glycemic control and treatment of cardiovascular risk factors for patients.[32] Nonetheless, the average levels of glycemic control, whether observed in university clinics or in community settings did not achieve desired levels of glycemic control in the majority of patients. Similarly, drugs directed for the treatment of chronic hypertension (ace inhibitors) and the statins for treatment of plasma lipid levels are contraindicated in pregnancy; this limits treatment options for these conditions. With these considerations in mind, it is prudent to intervene early in the onset of type 2 diabetes with measures designed to prevent overt glucose intolerance, dyslipidemia, and hypertension.

Known risk factors for the development of type 2 and gestational diabetes include a positive family history of type 2 diabetes and obesity,[33,34] insulin resistance and hyperinsulinemia,[35–37] impaired glucose tolerance (IGT),[38,39] and gestational diabetes as well as ethnicity, that is, Mexican–American.[40–44] In high-risk individuals, that is, patients with IGT or gestational diabetes mellitus (GDM), the presence of additional risk factors such as a family history of diabetes, obesity (body mass index [BMI] >27), certain ethnic backgrounds (i.e., American Indian, Mexican–American), and/or associated hypertension and dyslipidemia, the rate of progression toward type 2 diabetes may be as high as 5%–10% per year.[8]

The annual rate of progression to type 2 diabetes from gestational diabetes is calculated using the mean follow-up period and total incidence of type 2 diabetes in a given year. Studies have attributed an annual progression rate from a low of 0.5% (Stowers et al.[45]) to a high of 7.5%. The latter figure most likely represents a significant overestimation because of the use of actuarial projections. For most studies, the rate of progression to type 2 diabetes is about 2%–3% per year.[46]

The presence of obesity is a major factor that influences the rate of progression and its presence causes a twofold increase in the incidence of overt type 2 diabetes in patients with previous GDM.[47,48] Obesity, excessive weight gain during pregnancy, and/or failure to lose the excessive weight postpartum, ethnic background (especially Hispanic origin),[49,50] severity of fasting hyperglycemia during pregnancy, presence of IGT postpartum,[51,52] and positive family history of type 2 diabetes[53] have all been shown to increase the incidence of overt type 2 diabetes in women with gestational diabetes. With the above considerations in mind, the person at highest risk to develop type 2 diabetes within the shortest period would be the gestational diabetic woman who is obese, has a positive family history of type 2 diabetes, has a fasting plasma glucose concentration greater than 95 mg/dL during pregnancy, has IGT postpartum, and has an ethnic background shown to be associated with an increased incidence of type 2 diabetes (Table 31-1).

PATHOPHYSIOLOGY OF TYPE 2 DIABETES

Type 2 diabetes is a chronic, progressive, and incompletely understood metabolic disease defined by the presence of chronic hyperglycemia.[54] Although resistance to some actions of insulin and inadequate secretion of insulin for the given metabolic state are the critical abnormalities in type 2 diabetes, several other factors contribute to the hyperglycemic state such as endothelial cell dysfunction.[3] Insulin resistance is typically present for some years before diagnosis, manifested as diminished stimulation of glucose transport in muscle and adipose tissue and inadequate suppression of glucose production in the liver in response to insulin. However, euglycemia is maintained as long as β cells secrete higher amounts of insulin. Over time, insulin levels decline because of the decreased number of β cells and their diminished secretory capacity.[4,54–56]

Longitudinal studies involving Pima Indians and other populations have shown a 50% or greater decrease in maximal β-cell function at diagnosis; abnormal postprandial suppression of glucagon secretion also occurs. β-cell failure is mediated by genetic factors and exposure to chronically elevated levels of blood glucose (glucotoxicity) and free fatty acids (lipotoxicity). Older age, amyloid fibrils in islets, and chronically high rates of

TABLE 31-1 Risk Factors for Type 2 Diabetes

- Age ≥ 45 years
- Overweight (BMI ≥ 25 kg/m2[a]
- Family history of diabetes (i.e., parents or siblings with diabetes)
- Race/ethnicity (e.g., African-American, Hispanic-American, Native American, Asian-American, and Pacific Islanders)
- Previously identified IFG or IGT
- History of GDM or delivery of a baby weighing >9 lb
- Hypertension (≥140/90 mm Hg in adults)
- HDL cholesterol ≤35 mg/dL (0.90 mmol/L) and/or a triglyceride level ≥250 mg/dL (2.82 mmol/L)
- Polycystic ovary syndrome
- History of vascular disease
- High parity

[a]May not be correct for all ethnic groups.

Source: Modified from ADA Clinical Practice Recommendation 2005.

insulin secretion also perform mechanistic roles. The majority of genetic abnormalities that have been identified in patients with type 2 diabetes are related to β-cell function.[57] Insulin resistance and interrelated β-cell dysfunction and failure are the core pathologic defects in type 2 diabetes. Early in the course of the disease, insulin levels are elevated in an attempt to compensate for the increased insulin resistance of muscle/fat and hepatic tissues. As the disease progresses, insulin levels drop as the β-cells decline in function.[4,58,59] The disease progresses to hyperglycemia, which, if left untreated, leads to serious complications involving many major organ systems. Once hyperglycemia is identified, a disruption of the normal relationship between β-cell function and insulin sensitivity is established. The United Kingdom Prospective Diabetes Study (UKPDS) showed that type 2 diabetes is a progressive disease that stems from decline in β-cell function (Figure 31-1).[60]

There is a hepatic defect, which is characterized by excessive basal glucose production despite elevated fasting insulin levels and impaired suppression of hepatic glucose production in response to an incremental increase in plasma insulin concentration.[4] A defect in muscle glucose uptake has been demonstrated with leg and forearm catheterization techniques and has been shown to involve the pathways of both glucose oxidation and nonoxidative glucose disposal. In light of these acquired defects, it is obvious that the study of individuals with significant fasting hyperglycemia is unlikely to reveal the basic metabolic defect(s), which characterize the diabetic genotype and which are responsible for the initiation of the demise of glucose tolerance.[4]

1. Insulin Secretion. Loss of the first phase of insulin secretion develops early (fasting plasma glucose >115 mg/dL) in the natural history of type 2 and impaired second phase insulin secretion is present in the majority of type 2 diabetic individuals with fasting plasma glucose levels in excess of 160–180 mg/dL.[61–63] However, before the onset of IGT, the first and second phases of insulin secretion are increased, and conversion from normal to IGT is associated with the development of severe insulin resistance. A similar sequence of events occurs during the development of IGT in the rhesus monkey.[64]

2. Insulin Resistance. Impaired insulin action is a characteristic feature of type 2 diabetes. Insulin resistance involves the liver, muscles, and adipose tissue.[4,65]

Liver. Hepatic insulin resistance is characterized by excessive basal glucose production despite the presence of elevated fasting plasma insulin levels. The increase in fasting plasma glucose concentration in type 2 diabetics with overt fasting hyperglycemia (>126 mg/dL) is closely correlated with the increased rate of basal hepatic glucose production. This observation has led investigators to conclude that increased basal hepatic glucose production is a major, if not the primary, cause of fasting hyperglycemia in type 2 diabetes. Studies have shown that essentially the increased rate of hepatic glucose release results from accelerated gluconeogenesis, without any significant change in glycogenolysis. This increase in gluconeogenesis is due to an increased conversion of lactate, alanine, and glycerol to glucose. In mild type 2 diabetics with fasting plasma glucose concentrations less than 126 mg/dL, the absolute rate of hepatic glucose production is not increased, although evidence suggests that even in these individuals there is a shift from glycogenolysis to gluconeogenesis.[66–68]

Muscle and Adipose Tissue. Using a variety of techniques, including the insulin clamp, minimal model, and insulin suppression test, numerous studies have documented the presence of moderate-to-severe insulin resistance in peripheral tissues in type 2 diabetic subjects. Muscle has been shown to represent the primary tissue responsible for the defect in insulin action and the involvement of the pathways of both glucose oxidation and nonoxidative glucose disposal. Although fat tissue is resistant to insulin in these subjects, only small amounts of glucose load is disposed of by adipocytes; muscles are primarily

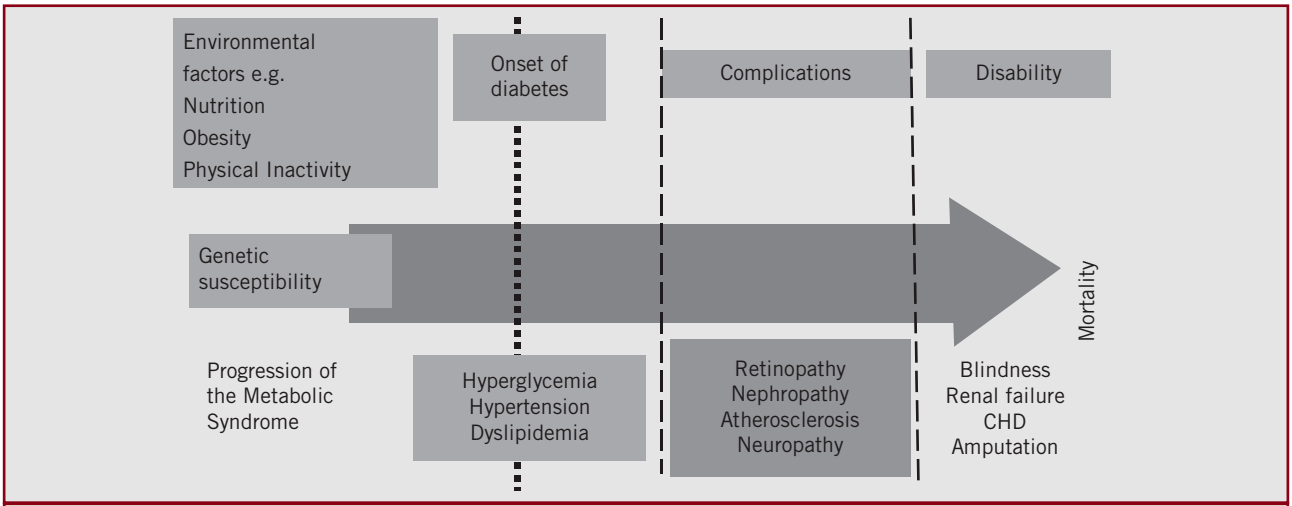

Figure 31-1 Pathogenesis of type 2 diabetes mellitus.

responsible for insulin-stimulated glucose uptake in humans. Both glucose oxidation (measured with indirect calorimetry) and nonoxidative glucose disposal are reduced in type 2 diabetes. From the quantitative standpoint, the decrease in nonoxidative glucose disposal is much greater than the defect in glucose oxidation and has been observed more consistently. The rate of nonoxidative glucose disposal agrees closely with the rate of muscle glycogen synthesis, as measured by nuclear magnetic resonance spectroscopy.[69]In summary, there are disturbances in all major pathways of glucose homeostasis (glycogen synthesis, glucose oxidation, hepatic glucose production) in type 2 individuals with overt fasting hyperglycemia.

At the cellular level, several mechanisms have been implicated in insulin resistance including a decrease in the number of insulin receptors on insulin target tissues, impaired tyrosine kinase activity, diminished glucose transport and phosphorylation, impaired glycogen synthesis, and defects in glycolysis and glucose oxidation. Insulin resistance appears to be the hallmark of type 2 diabetes. It appears early in the natural history of the disease but is offset by the presence of hyperinsulinemia. The insulin resistance is characterized by defects in both muscle and liver. Only later in the natural history of type 2 diabetes, when the compensatory increase in insulin secretion begins to fail does fasting hyperglycemia and overt type 2 diabetes develop.

On the basis of the above review of the pathogenesis of type 2 diabetes, interventions designed to enhance insulin sensitivity would appear to be most effective in the prevention of the disease. As increased physical activity and weight loss also enhance insulin sensitivity, these nonpharmacological interventions should be part of any primary prevention trial for type 2 diabetes.[70,71] Recently, Newsom et al.[72] reported that a relatively modest single session of exercise in obese adults improved insulin sensitivity the next day, and a reduction in systemic fatty acid uptake in the several hours after exercise may be important for this effect. Once the diabetic state has become fully established and hyperglycemia develops, all aspects of glucose homeostasis are disrupted and it is not possible to ascertain which defects are primary and which are acquired. Hyperglycemia per se can lead to acquired disturbances in insulin secretion.[4,73]

The Insulin Resistance Syndrome

A contemporary catchphrase in cardiology and diabetes discourse is metabolic syndrome. As many as 47 million Americans may have this cluster of medical conditions. People with the syndrome have nearly a 3% greater risk of developing clogged coronary arteries. Other studies have found that those who have the syndrome are twice as likely to have a heart attack as healthy individuals; four to five factors quadruple the risk of heart attack and raise the risk of diabetes.[37,74–76] The syndrome, also known as syndrome X, is a collection of potentially lethal metabolic abnormalities that include glucose intolerance, central obesity, hypertension, dyslipidemia, hyperinsulinemia, hypertriglyceridemia, and hypertension. These disorders serve to identify patients at significant risk for development of both cardiovascular disease (main cause of death in diabetic patients) and type 2 diabetes.[77]

In clinical practice, no single test diagnoses the condition. A formal definition of the insulin resistance syndrome (IRS) was devised for nonpregnant individuals[78] and can be diagnosed if any of the three of the following criteria are present: abdominal obesity (waist circumference >102 cm [40 in] for men and more than 88 cm [35 in] for women; triglyceride levels of 150 mg/dL (1.7 mmol/L) or higher; high-density lipoprotein (HDL) cholesterol lower than 40 mg/dL (1 mmol/L) in men and lower than 50 mg/dL (1.3 mmol/L) in women; blood pressure of 130/85 mm Hg or higher; and fasting glucose level of 110 mg/dL (6.1 mmol/dL) or higher. Two similar definitions were suggested by the American Association of Clinical Endocrinology (AACE) and the WHO. Approximately 25% of populations worldwide meet the criteria for the diagnosis of metabolic syndrome.

It is surprising that despite the acceptance of the syndrome, to date, few studies have addressed its impact in pregnancy. The physiological and metabolic changes accompanying pregnancy have profound effects on the mother. Yet no specific criteria for the pregnant state have been established. It is safe to assume that many GDM women and a fair segment of pregnant nondiabetic women (e.g., obese) would be classified as metabolic syndrome postpartum. Currently, the perinatal impact of the syndrome remains unknown. The criteria for metabolic syndrome in nonpregnancy cannot be accurately used in pregnancy. For example,

abdominal circumference is continually increasing; lipid and glucose metabolism changes as part of the normal physiology of pregnancy and pregnancy in and of itself is considered an insulin resistant state. These qualifiers question the validity of the definition of metabolic syndrome during pregnancy. Furthermore, because of the paucity of an accurate definition during pregnancy, it is impossible to measure the short-term outcome of the syndrome. If you cannot measure it, you cannot manage it. The problem of diagnosing without an established diagnosis is putting the cart before the horse. It has led to unnecessary labeling as well as overtreating and/or undertreating these women. We need to address our efforts to create diagnostic thresholds (correlated normality) for lipid, glucose, and other factors associated with type 2 and metabolic syndrome in pregnancy.

An insight into the impact of metabolic syndrome in pregnancy was suggested by Meyers-Seifer and Vohr.[79] They investigated lipid levels in women with previous GDM at 5–6 years postpartum. Their study showed that mean total cholesterol, triglycerides, low-density lipoprotein (LDL), glucose, and systolic blood pressure were significantly higher among GDM women compared to nondiabetic controls. In another study, obesity and GDM in a prior pregnancy were found to be a significant risk factor for development of the IRS over time. The authors concluded that early detection of markers of IRS is vital for possible prevention of type 2 diabetes and cardiovascular adverse events in women.[80] Bo et al. studied women with normal screening test, abnormal screening test with normal oral glucose tolerance test (OGTT), one abnormal value on the OGTT and gestational diabetes. The prevalence of metabolic syndrome was 0%, 4.9%, 20%, and 18%, respectively. They concluded that metabolic syndrome in mid-pregnancy was an independent predictor of macrosomia in women with any degree of gestational hyperglycemia; the oral glucose challenge test identifies pregnancies with metabolic abnormalities and adverse neonatal outcomes also in the presence of a normal OGTT.[81] Enhanced recognition of the population at risk and more aggressive treatment protocols are mandatory if patients are to be spared the development of type 2 diabetes, coronary artery disease, and stroke. The foundation of the treatment needs to be a conceptual framework that addresses diet, exercise, as well as drug therapy.

MATURITY-ONSET DIABETES OF THE YOUNG

Maturity-onset diabetes of the young (MODY) is characterized by nonketotic diabetes, an autosomal dominant inherited disease that affects function of the β cells of the pancreas. MODY is a result of mutations on any one of at least six genes. This heterogeneous group of ailments usually affects children, adolescents, and young adults before age 25. The mutation of the genes not only disrupts β-cell function leading to diabetes mellitus but also causes abnormal functioning of the liver and kidneys. The many factors that influence insulin sensitivity such as infection, puberty, and pregnancy may set in motion the onset of and enhance hyperglycemia in MODY patients.[82] Patients with MODY have a family history of diabetes and will often display mild, asymptomatic hyperglycemia. Some will have mild fasting hyperglycemia for many years (no classic symptoms and therefore MODY remains undiagnosed until adulthood), whereas others may demonstrate varying degrees of glucose intolerance for many years before persistent fasting hyperglycemia necessitating pharmacological therapy.[83–87] According to current accounts, MODY may be responsible for 1%–5% of all cases of diabetes in the United States and many industrialized nations.[88] MODY patients are distinct from type 2 diabetes patients in that family history of the disease can be traced back 3–4 generations, early onset, and absence of obesity. Type 2 diabetic patients are often diagnosed with increasing frequency in adolescence, but the distinguishing feature is obesity.

MODY 2 (glucokinase gene related) is the ailment that displays impaired fasting glucose and IGT especially in children of all racial and ethnic groups with mild hyperglycemia and in women with GDM and a family history of diabetes.[89] Heterozygous mutations in glucokinase are associated with mild, nonprogressive hyperglycemia (blood glucose concentration 110–145 mg/dL [6.1–8.0 mmol/L]) and is treated with diet alone.[90,91] Approximately 50% of women who are carriers of the muted genes have GDM[92]; less than 50% have overt diabetes. Those who suffer from overt diabetes are generally obese and older adults. Approximately 2% of carriers require insulin therapy. There are few known diabetes risk factors with MODY 2.[93] Reduction in β-cell sensitivity to glucose as well as a defect in postprandial glycogen synthesis in the liver appear to cause hyperglycemia in glucokinase-related MODY patients. The heterozygous mutations are associated with MODY and GDM. They influence a reduction in birth weight of 500 g or more, possibly because of their effect on fetal insulin secretion.[94,95] The homozygous mutations cause complete glucokinase deficiency with an accompanying permanent neonatal diabetes characterized by low birth weight, severe diabetes, and the necessity to administer insulin within a few days postpartum.[96] There is an increase in the threshold concentration of glucose needed to stimulate insulin secretion from about 90 mg/dL (5.0 mmol/L) to approximately 108–126 mg/dL (6.0–7.0 mmol/L). In addition, patients with MODY 2 have slightly increased basal and postprandial plasma glucose concentrations.[94]

Mutations in the hepatocyte nuclear factor (HNF)-4α gene (MODY 1) and mutations in the HNF-1α gene (MODY 3) are comparable. MODY 1 and 3 have similar mild elevations in fasting plasma glucose concentrations; they have higher plasma glucose concentrations two hours after glucose administration than do persons with MODY 2.[90] MODY 1 and 3 tend to increase over time and are associated with a progressive decrease in insulin secretion. Therefore, these patients tend to need oral hypoglycemic drugs or insulin (30%–40%). Mutations in the gene that encodes insulin promoter factor (IPF)-1 are not usually associated with MODY 4 and most of the information related to this condition is based on data from a single family.[97] MODY 5 is the result of mutations in the gene encoding HNF-1β that is characterized by diabetes and renal cysts.[98]

Today it is possible to identify genes responsible for MODY. Scientists can identify family members who have inherited specific mutations even before onset of carbohydrate intolerance. It is recommended that type 1 diabetic patients with a prominent familial history of the disease undergo genetic diagnosis as an appreciable proportion of these patients have been found to carry the HNF-1α mutation. The diagnosis of this gene mutation rather than of type 1 diabetes may ultimately enhance prognosis for these patients.[99,100] Obstetrician see women in adolescence and during their reproductive years, the period of MODY occurrence.

His (her) awareness of this phenomenon and its diagnosis may result in improved short- and long-term outcomes for mothers and infants.

IDENTIFICATION OF TYPE 2 DIABETES IN PREGNANCY

Type 2 diabetes has the highest prevalence among the different diabetic types. It is often asymptomatic in its early stages and can remain undiagnosed for many years. The prevalence of type 2 diabetes in pregnancy has been difficult to ascertain for many reasons. In research studies, pregestational diabetes includes patients with type 1 and type 2 diabetes without differentiation. Specific population subgroups have a much higher prevalence of the disease than the population as a whole. These subgroups have certain attributes or risk factors that either directly cause diabetes or are associated with it. When a pregnant woman is taking insulin, the assumption is that she has type 1 diabetes. This assumption may be valid for countries such as Sweden and Finland where the prevalence of type 1 diabetes is high. However, this would be a mistaken assumption for other countries such as Japan, the United Kingdom, and the United States in which the prevalence of type 2 diabetes is higher than that of type 1 and about 75% of women with prepregnancy diabetes have type 2 diabetes.[101]

The risk for developing type 2 diabetes increases with age, obesity, and lack of physical activity. In general, type 2 diabetes is more common with a family history of diabetes and in certain racial/ethnic groups. It occurs more frequently in women with prior GDM or polycystic ovary syndrome and/or metabolic syndrome (hypertension, dyslipidemia, IGT, or impaired fasting glucose). The greater number of risk factors increases the odds that the individual will develop type 2 diabetes (Table 31-1).[102]

Screening for type 2 diabetes should ultimately be based on clinical judgment. Screening should be performed on asymptomatic patients in three-year intervals beginning at age 45, especially in obese women (BMI >25). However, testing for diabetes should be considered at a young age and at more frequent intervals in subjects who are overweight or who have one or more additional risk factors. The fasting plasma glucose is the recommended screening test. Fasting plasma glucose ≥126 mg/dL (7 mmol/L) is an indication for retesting on a different day for confirmation of the diagnosis. The 75-g OGTT may be necessary for the diagnosis of diabetes when the fasting plasma is normal. A two-hour post-load of ≥200 mg/dL (11.1 mmol/L) is considered a positive test but should be confirmed on an alternate day.

Nondiabetic individuals with fasting plasma glucose ≥100 mg/dL but <126 mg/dL are considered to have impaired fasting glucose, and those with the two-hour value on the OGTT ≥140 mg/dL (7.8 mmol/L) but >200 mg/dL are defined as having IGT. Both of these categories are referred to as prediabetes. Normal glycemia is defined as plasma glucose <100 mg/dL (5.6 mmol/L) and two-hour post load value of <140 mg/dL on the OGTT.[102] Pregnancy is characterized by a lower level of fasting plasma glucose and a higher level of postprandial. Therefore, in pregnancy, patients with fasting glucose levels >100 mg/dL but <126 mg/dL who would be categorized in the nonpregnant state as impaired glucose tolerant, in fact can be a masked type 2 diabetes in pregnancy. Again, this shows the overlap in the diagnosis criteria among normal, GDM, IGT, and type 2 diabetes.

Patients with symptoms of marked hyperglycemia that include polyuria, polydipsia, weight loss, and blurred vision should receive diagnostic testing for diabetes. Other patients need to be screened for potential complications of diabetes or with any other clinical presentation in which diabetes is included in the differential diagnosis. A casual plasma glucose level of ≥200 mg/dL with symptoms is considered a diagnostic for GDM. The HbA1c is not universally recommended for screening or diagnosis of diabetes (Table 31-2).[102]

GDM patients are often women who have gone undiagnosed for type 2 diabetes and are brought to the attention of the medical community when screened in pregnancy. In areas where there is efficient universal screening, they are diagnosed before 20 weeks' gestation and may have fasting hyperglycemia; they may display symptoms of type 2 diabetes when tested postpartum. Inefficient and ineffective screening mechanisms may cause women to go undiagnosed throughout pregnancy. The inability to make accurate estimations of prevalence makes it impossible to determine the frequency of various maternal and fetal complications and the economic and social implications they engender.

PREVALENCE OF TYPE 2 DIABETES IN PREGNANCY

Several studies have measured the prevalence of type 2 diabetes in pregnancy. The prevalence of the disease is based on ethnicity, geographic region, obesity, and dietary habits of a given

TABLE 31-2 Criteria for the Diagnosis of Diabetes

- Symptoms of diabetes and causal plasma ≥200 mg/dL (11.1 mmol/L). (Casual as any time of day without regards to time since last meal. The classic symptoms of diabetes included polyuria, polydipsia, and unexplained weight loss.
  OR
- FPG ≥126 mg/dL (7.0 mmol/L). No caloric intake for at least eight hours.
  OR
- 2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.

In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The OGTT is not recommended for routine clinical use, but may be required in the evaluation of patients with IFG (see text) or when diabetes is till suspected despite a normal FPG as with the postpartum evaluation of women with GDM.

Source: Modified from ADA Clinical Practice Recommendation 2005.

population. However, the majority of studies showed approximately 10%–15% undiagnosed type 2 diabetes within the GDM population.[11,51,103–105] Three studies were population specific and may not be generalizable to the population at large. In a prospective study of 811 pregnancies in the Pima Indians of Arizona, 6.3% were known to have diabetes before pregnancy.[106] An additional study of type 2 diabetes (diagnosed before pregnancy) in the Ojibwa-Cree nation of northwestern Ontario, Canada, demonstrated a prevalence of 3.2%.[107] A prevalence of 3.4% for type 2 diabetes was found in women of the Tohono O'odham nation in southern Arizona in the first 20 weeks' gestation.[108] Engeigau et al.[109] in a broad population-based survey performed in the United States suggested an increasing prevalence of type 2 diabetes in pregnancy. They estimated that about 0.2%–0.5% of all pregnancies were complicated by pregestational diabetes (type 1 or type 2) and that type 2 diabetes accounted for 65% in the year of the study, that is, 1995, compared with only 26% in 1980. These studies demonstrated mainly ethnic-specific populations and not a cross section of the population. Therefore, the results of these studies represent the tip of the iceberg but the submerged glacial mass remains unknown.

MATERNAL AND FETAL COMPLICATIONS OF TYPE 2 DIABETES

The increasing prevalence of type 2 diabetes in pregnancy is being recognized as representing at least as significant a risk to both mother and baby as does type 1 diabetes. It may ultimately enhance pregnancy complications for both mother and infant.

Maternal Complications

Type 2 diabetes currently contributes to the increased rate of adult onset loss of vision, renal failure, and amputations more than any other disease. The majority of patients are obese and have hypertension and dyslipidemia resulting in a two- to fivefold higher risk of cardiovascular disease in which 70% of the patients die.[110,111] The average delay of 4–9 years till diagnosis of type 2 diabetes translates into approximately 20% of patients who have some evidence of microvascular or neurological diabetic complications at the time of diagnosis.[5,112] In the United States, the estimated costs of providing care for diabetes is at least $100 billion annually with half attributable to direct cost.[113,114]

The complications associated with the disease are a result of its duration in addition to the average level of chronic glycemia. HbA1c is a retrospective measure (10–12 weeks) of the level of glycemic control. As it is a retrospective measure, it can be used as a predictor for maternal medical complications. However, its predictability for fetal disease (excluding anomalies) is minimal.[115–117] Two classic studies established the role of intensive therapy in the reduction of long-term complications in nonpregnant patients with type 2 diabetes. They demonstrated that metabolic goals in type 2 patients with HbA1c of <7%, average fasting plasma glucose of 90–130 mg/dL and post-meal plasma glucose levels of <180 mg/dL, will result in significant decreases in patient long-term complications.[102,118–120] The intensified management approach (reducing LDL and triglyceride levels, increasing HDL levels), control of hypertension (with two or more medications) will significantly decrease maternal medical complications. However, the level of glycemia required for this effect to occur will not be sufficient to prevent pregnancy-related maternal (preeclampsia) and fetal complications (perinatal mortality, macrosomia, etc.)

There is paucity of studies addressing type 2 diabetes in pregnancy and maternal complications. The majority of studies does not distinguish between type 1 and type 2 diabetes, although they recognize the existence of both in their studies yet combine them for the sake of sample size and paucity of information for each group.[121–130]

Many studies are based on small sample sizes and report rates of hypertensive disorders such as chronic hypertension and preeclampsia but do not specifically address nephropathy, retinopathy, and neuropathy. In addition, the majority of studies do not include specific data on level of glycemic control (method, definitions). Not surprisingly, there are high rates of chronic hypertension (obesity) and preeclampsia (probably because of severity of the disease and poor glycemic control). In 1989, the St. Vincent Declaration set as one of its targets the improvement in pregnancy outcome compromised by diabetes so that the risks would approach those in the nondiabetic population. Despite this lofty goal, the majority of studies on type 1 diabetes or undistinguished preexisting diabetes reporting national data or data from large centers, failed to demonstrate significant improvement. In general, the rate of medical complications is similar in type 1 and type 2 diabetes.[131]

The major problem in the evaluation of complication rates for types 1 and 2 diabetes during pregnancy is that data are derived from nonpregnant older patients; women of reproductive age are younger and, therefore, the rate of complications may be different. Research shows that 60% of patients with type 2 diabetes do not increase exercise levels following a diabetes diagnosis and 50% do not alter their diets. The figures result from a survey of 652 patients with type 2 diabetes and 337 physicians from the United Kingdom, United States, Spain, India, Japan, and Brazil. The survey aimed to explore why patients with the type 2 diabetes fail to reach treatment goals. Alarmingly, 75% of the patients surveyed were not concerned about the complications of diabetes. A contributing factor is that only 50% of patients were aware of being told of the risks of complications at their diagnosis. The survey suggests that patients need to repeatedly be made aware of the risk of complications. It is understandable that shock and anxiety at the news of such a diagnosis may make it harder for patients to fully absorb the implications of the condition. Lifestyle interventions are important in type 2 diabetes management in order to reduce the risk of health complications and delay the introduction of stronger diabetes medications such as insulin.

The Diabetes and Aging Study was funded by the National Institute of Diabetes and Digestive and Kidney Diseases and the University of Chicago. They found that patient age and disease duration independently determine the clinical course of the disease among adults aged 60 to 80-plus years. The research analyzed data from the Kaiser Permanente Northern California Diabetes Registry of 72,310 diabetic patients aged 60 years and older at baseline in 2004. The mean patient age was 71 years, and about 15% of the study population was aged 80 years and older. The cohort was ethnically diverse and had equal access to health care; most patients were receiving statins and angiotensin-converting enzyme (ACE) inhibitors appropriately. The study participants

were followed for up to seven years (mean follow-up: 5.4 years) for acute hyperglycemic events requiring hospitalization; acute hypoglycemic events requiring emergency department visits or hospitalization; microvascular complications such as severe eye disease, incident end-stage renal disease, peripheral vascular disease, and amputation; nonfatal cardiovascular complications such as myocardial infarction, coronary artery bypass graft surgery, angioplasty, ischemic or hemorrhagic stroke, and congestive heart failure; and fatal complications of any kind.

The cardiovascular complications of diabetes are considered the most common as well as the most serious in patients of all ages, and preventing them by concentrating on glycemic control has been the mainstay of diabetes management. But the above large cohort study showed that among older patients and those with longer disease duration, hypoglycemia rates approached those of coronary artery disease. This finding indicates that the core focus of glycemic control is inappropriate for a substantial number of older diabetes patients. "To the extent that hypoglycemia is an adverse effect of treatment, its emergence as a dominant 'complication' raises serious concerns about the acceptable limits of iatrogenesis." Both patient age and duration of type 2 diabetes had a significant, independent effect on which complications were likely to arise. Most notably, the risk of hypoglycemia rose markedly with increasing age and duration of disease, so that it outpaced both coronary and cerebrovascular events as the most common serious complication in this subset of the population. Hypoglycemia was even fairly frequent among younger patients; it was the fourth most common complication among patients in their 60s and the third most common among patients in their 70s. The rate of hypoglycemic events ranged from a low of 3.0/1000 person-years among the youngest patients with the shortest duration of disease to a high of 19.6/1000 person-years among the oldest patients with the longest duration of disease. The corresponding rates of coronary artery disease events were 8.5 and 24.1 per 1000 person-years. This suggests that intensive glycemic control *may not* be a helpful treatment goal and may even be harmful to the latter group. In addition, among the oldest patients who had a long duration of diabetes (more than 10 years) the rate of acute hyperglycemic events was only 2.35/1000 person-years. The distinctive clinical course of different patient strata supports recommendations to individualize glycemic targets among older people.[132]

The TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) studies may be preferable as a data source of diabetes in pregnancy. This study controls for age, ethnicity, and similar duration of the disease in the nonpregnant state. The series of studies emphasized the increasing burden of type 2 diabetes in youth and adolescents. In one study, the authors sought to determine the prevalence of retinopathy in 517 youth with type 2 diabetes of 2–8 years duration. They concluded that the prevalence of retinopathy and its association with HbA1c and diabetes duration is similar to that previously reported in youth with type 1 diabetes and in adults with type 2 diabetes of known duration. The mechanism underlying the reduced risk of retinopathy in the most obese individuals is unknown. Follow-up of this cohort will help define the natural history of retinopathy in youth with type 2 diabetes.[133] The prevalence of early retinopathy in young people with a mean duration of type 2 diabetes of 4.9 years was 13.7%. This is higher than previously reported in young Pima Indians, in whom retinopathy was detected only after age 20 and who had diabetes for five years. Retinopathy in that study was determined by dilated direct ophthalmoscopy, rather than by standardized fundus photographs assessed by skilled graders.

In the SEARCH study, the prevalence of retinopathy using retinal photography was 17% for type 1 diabetes and 42% for type 2 diabetes. However, participants in the SEARCH study had known diabetes duration of five years (mean duration 7.2 years) and were older (mean age 21 years). In a small Australian study of adolescents with type 2 diabetes, researchers found a retinopathy prevalence of only 4%. Differences in methodology in these studies make direct comparisons difficult. However, retinopathy prevalence in adults who developed diabetes on follow-up in the Diabetes Prevention Program was 15.5% after slightly more than three years of diabetes. As in adults, increased prevalence of retinopathy in TODAY participants was associated with older age, longer diabetes duration, and glycemic control as assessed by HbA1c. The most severely obese individuals had decreased retinopathy. An association of lower weight or BMI with increased retinopathy has been reported previously in adults with type 2 diabetes and has been attributed to poor diabetes control. In one study[10] of 207 type 2 diabetics, nonproliferative retinopathy was seen in 28% of women, proliferative retinopathy (undiagnosed before pregnancy) found in 4.3%. A small number of women (1.4%) had overt diabetic nephropathy, whereas preeclampsia was high in both groups (26.5% in the patients with type 1 and 30.9% in women with type 2 diabetes). The risk of diabetic complications from type 2 diabetes in pregnancy already warrants that these women receive careful assessment and follow-up.[134]

The prevalence of hypertension and microalbuminuria increased over time among adolescents with type 2 diabetes regardless of diabetes treatment. The greatest risk for hypertension was male gender and higher BMI. The risk for microalbuminuria was more closely related to glycemic control. Among adolescents with type 2 diabetes, there is limited information regarding the incidence and progression of hypertension and microalbuminuria. Hypertension and microalbuminuria assessments made during the TODAY clinical trial were analyzed for effect of treatment, glycemic control, gender, and race/ethnicity.

The TODAY trials demonstrated that combination therapy with metformin plus rosiglitazone provided superior durability of glycemic control compared with metformin alone, with significantly lower treatment failure rates (38.6% vs. 51.7%), and metformin plus lifestyle was intermediate. The beneficial change in insulin sensitivity and the resultant lower burden on β-cell function achieved in the first six months with metformin plus rosiglitazone appear to be responsible for its superior glycemic durability over metformin alone and metformin plus lifestyle. However, initial β-cell reserve and HbA1c at randomization are independent predictors of glycemic durability. Therefore, efforts to preserve β-cell function before significant loss occurs and to reduce HbA1c may be beneficial in the treatment of youth with type 2 diabetes.[135] However, the use of rosiglitazone is currently being debated since no study to date has evaluated its safety and efficacy in pregnancy. This leaves us with the option to manage type 2 diabetes with metformin in combination with insulin and/or sulfonylurea medications; however, this combination, too, has also not been tested in pregnancy.

Two major complications related to level of glycemia during pregnancy are diabetic ketoacidosis and hypoglycemia. Hypoglycemia is associated with type 1 diabetes and less common in GDM and type 2 diabetes. Both complications are described in detail in other chapters. Briefly, diabetic ketoacidosis onset in pregnancy will occur at lower glucose levels, and, in comparison to nonpregnant women, often progresses more rapidly. With early detection of precipitating factors (i.e., infection, intractable vomiting, inadequate insulin management or inappropriate insulin cessation, and steroid administration for fetal lung maturation), prompt hospitalization, and targeted therapy with intensive monitoring, morbidity and mortality can be reduced. Management principles include aggressive volume replacement, initiation of intravenous insulin therapy, correction of acidosis, correction of electrolyte abnormalities, and management of precipitating factors, as well as monitoring of maternal-fetal response to treatment. A chain of events during a diabetic ketoacidotic episode can self-perpetuate into a vicious cycle. The elevated glucose levels in the intravascular space create an osmotic gradient, resulting in marked diuresis that in turn leads to a profound state of dehydration and hypovolemia. Hyperglycemia and acidosis are intensified because it promotes the activation of other counter regulatory stress hormones (i.e., growth hormone, cortisol). Sodium levels can become abnormally low as a result of the osmotic diuresis. In addition, electrolyte salts containing sodium, potassium, and phosphorus become bound to anions from keto acids in the bloodstream and are excreted in the urine. Protein breakdown (as a consequence of the perceived state of starvation) and decreased potassium cellular uptake resulting from the lack of insulin result in normal or elevated serum potassium levels in the presence of diminished total body potassium. To forestall morbidity and mortality, a multidisciplinary approach and continuous monitoring of the maternal response to therapy are critical. After viability, fetal monitoring is also indicated, and it is mandatory that maternal metabolic abnormalities be addressed before considering emergent delivery, because both maternal and fetal conditions will likewise improve.[136–141]

Euglycemic ketoacidosis was first described by Munro et al. in 1973 and is defined as severe ketoacidosis with a serum bicarbonate of 10 mEq/L or less in the absence of pronounced hyperglycemia (blood glucose <200 mg/dL). This level is twofold higher than the glycemic profile found in nondiabetic women. Therefore, the term euglycemia may be misleading and the complications may occur in mildly controlled patients. The condition can also occur in poorly controlled type 2 and GDM women. True euglycemic ketoacidosis is exceedingly rare, occurring in 0.8%–1.1% of all episodes (depending on the defining plasma bicarbonate concentration).[142–144] Diabetic ketoacidosis is a rare but serious complication of diabetes in pregnancy with deleterious consequences for both the mother and the fetus. Prompt recognition of precipitating factors, aggressive correction of volume depletion and electrolyte imbalance, and insulin administration are paramount in the management of diabetic ketoacidosis.

Fetal Complications

In 1989, the St. Vincent Declaration set as one of its targets the improvement in pregnancy outcome for women with diabetes so that the risks would approach those of the nondiabetic population. Despite the lofty goal, the majority of studies on type 1 diabetes or undistinguished preexisting diabetes reporting national data or data from large centers, failed to demonstrate significant improvement resulting in an over 20% prematurity rate, 26%–55% rate of large-for-gestational age infants, 15%–35% macrosomia, 4%–9% congenital malformations, and 2%–5% perinatal mortality (Table 31-3).[121,145–150]

TABLE 31-3 Preexisting Diabetes: Perinatal Outcome

	PTD	SGA	LGA	Macrosomia	Neonatal Complication	CA	Stillbirth	Perinatal Mortality
Sibai et al. '00 (MFMU/NICHD *n* = 462)	38%	6.3%	34.4%	15.4%	48.1%	NA	1.8%	3.9%
Evers et al. '04 (118 Hospitals-Netherland *n* = 289)	32%	3.0%	56%	25.3%	80.2%	8.8%	NA	2.8%
Lauenberg et al. '03 (Denmark *n* = 1361)	NA	NA	45%	35%	NA	NA	1.8	NA
Persson et al. '96 (Sweden *n* = 113)	21%	3.0%	26%	26%	15%	3.5%	NA	0%
Peck et al. '91 (UK *n* = 133)	NA	NA	38%	NA	16%	5.3%	NA	2.4%
Penney et al. '03 (Scotland National *n* = 213)	NA	NA	55%	NA	NA	6.0%	1.9%	2.9%
Diabetes in pregnancy group, France (*n* = 435)	38%	NA	NA	17.3%	NA	4.1%	3.5%	4.6%
Jovanovic '91 EDPS	NA	7.8%	29%	NA	NA	NA	NA	NA

There is paucity of available data on perinatal mortality in women with type 2 diabetes. However, one study suggested that the rate of perinatal mortality might be higher than that of women with type 1 diabetes.[151,152] In the study by Cundy et al.,[151] perinatal mortality was calculated over a 12-year period (1985–1997) in women (Maori or recent immigrants from Pacific Island nations) with type 2 diabetes attending a diabetes clinic in Australia. The region-specific nature of the study again may preclude generalizability. Perinatal mortality (late fetal death, 28 weeks to term) was significantly higher than in women with type 1 diabetes. Maternal comorbidities including obesity, higher maternal age, higher frequency of hypertension, and low socioeconomic level may have also contributed to the increased mortality rate. This group presented later for care than did women with type 1 disease and were both smokers and obese. Obesity coupled with type 2 diabetes as well as delayed perinatal care has been associated with an increased risk of late fetal death, fetal macrosomia, and preterm delivery. The risk for the fetus for the above complications is not equal for all fetuses. The risk will be dependent on the glycemic level. In addition, because of the number of undiagnosed type 2 patients in GDM, the fetuses are at greater risk for death.

Other published works report perinatal mortality ranging from 4/1000 to 81/1000. Zhu et al.[153] and Coetzee et al.[154] demonstrated no significant difference in perinatal mortality between patients with type 2 and type 1 diabetes, whereas the study by Sacks et al.[155] reported four perinatal deaths in 113 patients with type 2 and none in the 46 patients with type 1 disease. Sacks et al. also found no significant differences in the rates of macrosomia, caesarean section, shoulder dystocia, and neonatal hypoglycemia between the mothers with type 1 and type 2 diabetes. When confirmation from other studies of these findings and corroboration that the outcomes of women with type 2 are similar to those of women with type 1, similar concern to that afforded women with type 1 diabetes will be shown in women with type 2 diabetes and their infants. In fact, a review of the few studies addressing type 2 diabetes in pregnancy revealed similar adverse outcome rates to type 1 diabetes (Table 31-4).[156–160] Recently, Tennant et al.[125] reported in a large study that the incidence of fetal death, infant death, and congenital malformation showed no difference between types 1 and 2 diabetics in a North England population. A unique feature in the study was that the perinatal mortality rate was calculated with the exclusion of congenital malformations. Overall, the relative risk for perinatal mortality was two- to fourfold higher than in the nondiabetic population with fetal death (RR 4.56 [95% CI 3.42, 6.1], $P < .0001$) and infant death (RR 1.86 [95% CI 1.00, 3.46], $P = .046$). There was no difference in the prevalence of fetal death or infant death between women with type 1 diabetes and women with type 2 diabetes. Moreover, there was no evidence that the relative risk (RR) of fetal and infant death had changed over time ($P = .95$). The effect of this finding is largely moderated by glycemic control. In our program (unpublished data), we also found similar outcomes in neonatal size, lung complications, and neonatal intensive care unit admissions in type 1 and type 2 diabetic patients (Table 31-5).

Just as infants born of mothers with type 1 diabetes are at increased risk of congenital anomalies, so are infants of women with type 2 diabetes. A prospective study of pregnancies complicated by type 2 diabetes in predominately Hispanic women demonstrated a high rate of congenital anomalies in comparison to those who had not participated in a preconception diabetes care program.[161] Fifty-six of the 332 infants (11.7%) were born with major congenital anomalies, whereas the rate of congenital malformations in infants of nondiabetic women born in the same hospital during the same period was <2%. These malformation rates compared to those reported in studies of infants born to women with type 1 diabetes who had not received preconception care. The authors attributed poor glycemic control as the cause of the malformations. In the above study, maternal glycosylated hemoglobin concentrations at initial presentation for care were independently associated with the major malformations ($P = .0007$).

TABLE 31-4 Type 2 Diabetes Pregnancy Outcomes

	Coetzee '85	Dooley '98	Brydon '00	Dunne '03	Ozumba '04	Gunton '02
Mean birth weight	NA	4.075	NA	NA	NA	3407
Macrosomia	NA	62%	NA	9%	39%	
LGA	15%	NA	40%	32%	NA	36%
Stillbirth	37%	4%	4%	1.2%	14%	5.3%
Shoulder dystocia	NA	15%	NA	NA	NA	0
Congenital malformation	8%	8%	12%	11%	9.0%	NA
Jaundice	53%	38%	NA	NA	NA	NA
Hypoglycemia	12%	8%	NA	NA	NA	NA
Polycythemia	NA	NA	NA	NA	NA	NA
Respiratory distress syndrome	NA	4%	NA	NA	NA	NA
NICU	NA	NA	NA	37%	NA	NA
No. of patients	691	26	57	165	122	11

TABLE 31-5 Pregnancy Outcome in Type 2 Diabetes: The San Antonio Experience (1990–2000)

	Type 1	Type 2	*P*
Gestational age delivery	37 ± 3	38 ± 4	<0.13
NICU	13%	10%	<0.001
Respiratory support	17%	7%	<0.001
Lung complications	30%	23%	<0.09
No. of days intubation	9 ± 14	3 ± 8	<0.09
Neonatal hypoglycemia	18%	26%	ns
LGA (>90 percentile)	18%	23%	<0.05
Macrosomia (>4000 g)	9%	14%	<0.007
SGA (<10 per.)	14%	7%	<0.05
Shoulder dystocia	2%	6%	Ns

No difference in glycemic control was noted between women taking oral hypoglycemic agents during the first eight weeks of gestation and those on insulin or diet, suggesting that the oral hypoglycemic agents were not the cause of the malformations.

A study in the United Kingdom of mostly Indian women with type 2 diabetes reported twice the frequency of congenital malformations compared with type 1 diabetic women (12.2% vs. 6.1%). The authors ascribed poorer attendance for prenatal care, delayed booking for antenatal care, and failure to adhere to a strict regimen of glycemic control during organogenesis as contributing factors to the higher rate of congenital malformations.[157]

The rate of congenital anomalies in patients with type 1 diabetes can be reduced to that of the general population if good glycemic control is achieved at the time of conception. Although targeted levels of glycemic control have been achieved by women in certain academic centers, the reports from population studies show that clinicians have not been as successful in preventing congenital anomalies.[162,163] Population studies performed in Europe and the United States report rates of congenital anomaly and perinatal mortality significantly higher than that in the general population. In a study evaluating preconception education, 61% of the type 1 diabetic women had failed to achieve targeted levels of glycemic control at onset of pregnancy. Another study examining the reasons why women were not proactive in planning for pregnancies with improved glycemic control before conception, found that many socioeconomic variables contributed to their lax behavior.[164]

Cultural and socioeconomic factors compounded by minority or immigrant status often preclude women with type 2 diabetes in industrialized countries from accessing appropriate care for their disease. In addition to patients' reticent approach and as aware as they may be of complications because of type 1 diabetes in pregnancy, clinicians are not generally aware of the increased prevalence of type 2 diabetes in pregnancy and the attending complications. They have been trained to accept the dogma that women on diet therapy or oral hypoglycemic agents have "mild" diabetes and are, therefore, at less risk. This fallacy can lead to suboptimum care and follow-up, increasing the chance for poor glycemic control at the onset of pregnancy, and a subsequent increase in congenital anomalies.

Treatment Modalities for Type 2 Diabetes in Pregnancy

A 36-year-old woman at 16 weeks gestation with a two-year history of type 2 diabetes mellitus presents for care. She has no microvascular or macrovascular complications. Her family history is positive for type 2 diabetes and cardiovascular disease in her mother and older brother. On examination, her weight is 99.8 kg (220 lb), with a BMI of 37 and blood pressure 125/85 mm Hg. Her glycosylated hemoglobin level is 9.3%, serum creatinine level 1.0 mg/dL, LDL 88 mg/dL, HDL cholesterol 45 mg/dL, and triglyceride level 190 mg/dL. She does not have microalbuminuria. Her medications include metformin (500 mg twice daily) and glipizide (5 mg twice daily).

This patient presents several areas that require modification to optimize her care. The level of glycemic control is not satisfactory for pregnancy or for the nonpregnant state. She needs to be transferred to insulin therapy as oral agents will not achieve, in this patient, the desired level of glycemic control. The second problem is the inability to administer statins during pregnancy; thus, the only way to improve her status is to encourage diet and behavior modification both dependent on patient compliance. In addition, the hypertension needs to be brought under control with pregnancy-prescribed drugs. This patient will need a complete work-up to rule out potential congenital malformations with a plan for follow-up for fetal growth diversity and surveillance.

The main goal of all treatment modalities in type 2 diabetes is to delay or mitigate the complications of the disease. However, different management approaches need to be employed before conception and during pregnancy as some drugs are contraindicated during pregnancy. In addition, the glycemic goal to optimize pregnancy outcome are different prior and during pregnancy. The two main maternal complications fall into 2 groups: microvascular (retinopathy, nephropathy, and neuropathy) and macrovascular (ischemic heart disease, stroke, and peripheral vascular disease). The randomized UKPDS in nonpregnant individuals clearly demonstrated that intensified therapy (sulfonylureas or insulin) is superior to conventional therapy of diet and exercise alone (to decrease microvascular complications). However, the study showed that diabetes is a progressive disease and the efficacy of the medications decreased after five years. The UKPDS

demonstrated that each percentage point reduction in HbA1c reduced microvascular complications by 37%, diabetes-related endpoints by 21%, death related to diabetes by 21%, and myocardial infarction by 14%.[116]

The traditional approach to treatment of type 2 diabetes and gestational diabetes is based on a step-wise approach from the least invasive to pharmacological therapy. The first step involves diet and lifestyle modification to include exercise to achieve weight loss. Weight reduction of 2.3–4.5 kg (5–10 lb) can result in a significant decrease in the glucose profile.[165] The problem with this approach is twofold. This minimal weight reduction will not result in targeted glucose levels that are needed to optimize pregnancy outcome. Furthermore, weight reduction is not recommended in pregnancy even in obese patients. Thus, the hypocaloric diet to the extent of weight reduction may adversely affect the fetus. Ultimately, we seek to program the unborn child for the metabolic world his mother inhabits and the one in which he/she is expected to live and thrive.[166,167] Therefore, it is more efficacious to reserve a weight reduction diet for the pre- and postpartum periods. During pregnancy, a diabetic diet should be prescribed based on the principles designed for pregnancy.

The second step is the addition of oral agents if the patient is not yet on that regimen. This step is used mainly in type 2 nonpregnant diabetics; in pregnancy this approach will fail to achieve a level of glycemic control required to enhance pregnancy outcome in the majority of patients. Therefore, in type 2 pregnant women, insulin analog therapy is the preferred management.

Sulfonylureas and metformin are the most commonly used oral hypoglycemic agents. Both drugs lower glycosylated hemoglobin by approximately 1.5%. One problem with oral agents is the debate if these drugs can be used in the first trimester even if it appears safe to use glyburide and metformin throughout pregnancy. Combination therapy with these two drugs can significantly improve the level of glycemic control. However, is the improvement in glycemic control achieved in type 2 diabetes sufficient to protect the fetus from the effect of glucose toxicity? To date, as previously described, there is no data reporting achievement of outcome comparable to nondiabetic individuals. The physician must determine if using this drug will bring his patient with type 2 diabetes to a level of glycemia resulting in a healthy and viable child.

The next step is invoked if oral antidiabetic drugs fail to achieve level of glycemic control or the physician chooses to go directly to insulin therapy. Higher doses of insulin virtually always result in lower glucose levels. The problem is that insulin is not always used in the appropriate dose. The most commonly used therapy is to calculate insulin dose based on 1 unit/kg of body weight and thereafter to increase the dose as needed. Split injection for GDM and type 2 diabetic women is the most effective approach. The insulin pump should be used in type 1 diabetes. Insulin can also be administered in combination with sulfonylurea or metformin thus decreasing the overall insulin dose. However, no data has been forthcoming supporting this management combination.

SUMMARY

Now that we have been forewarned of the growing pandemic of type 2 diabetes and obesity in pregnancy, we need to become forearmed. Over the past few decades there has been no significant improvement in perinatal outcome complicated by diabetes mellitus (types 1 and 2). The recognition of modifiable risk factors such as maternal glycemic control using self-monitoring blood glucose in combination with pharmacological therapy (intensified therapy) and weight gain in pregnancy should enhance pregnancy outcome. The overemphasis and concentration on the nonmodifiable risk factors in pregnancy is a futile pursuit that may generate lively discussion but paucity of results. The focus needs to be in education for the care provider, that is, enhanced recognition of this growing entity and a heightened awareness of the need for prepregnancy counseling about preconception glycemic control. Another center of attention should be the dissemination of information to patients of the impending maternal and fetal risks of type 2 diabetes in pregnancy. This care would include antenatal care for surveillance of maternal diabetes complications as well as careful obstetric surveillance to improve maternal and fetal outcomes.

The incremental successes in the treatment of type 1 diabetes in the nonpregnant and pregnant states bode well for comparable success in assessing and treating type 2 diabetes in pregnancy The parallel thrusts must be in education for the care provider, that is, enhanced recognition of this growing entity and a heightened awareness of the need for prepregnancy counseling about preconception glycemic control. Another front would be the dissemination of information to patients of the impending maternal and fetal risks of type 2 diabetes in pregnancy coupled with an environment of cultural competence that empowers the patient to seek and receive appropriate care. This care would include antenatal care for surveillance of maternal diabetes complications as well as careful obstetric surveillance to improve maternal and fetal outcomes.

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Diabetic Ketoacidosis in Pregnancy

32

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An ounce of prevention is worth a pound of cure.

—Benjamin Franklin

Key Points

- Diabetic ketoacidosis (DKA) during pregnancy is an emergency medical situation with a high mortality risk for both mother and fetus
- DKA is more common with type 1 diabetes and under continuous subcutaneous insulin infusion (CSII) treatment but may be seen in patients with type 2 diabetes and gestational diabetes under conditions such as stress due to severe intercurrent illness
- DKA during pregnancy tends to develop more rapidly in comparison to the nonpregnant state; it may be characterized with only minor or no change in the glucose values
- Prevention of DKA can be achieved through patient education before and during pregnancy with emphasis on patients' awareness of the expected changes of insulin regimen during the different stages of the pregnancy
- Treatment protocols are based on correcting volume depletion, supplying insulin, correcting acidosis and electrolyte imbalance, and identifying and correcting any possible precipitating factor

INTRODUCTION

Diabetic ketoacidosis (DKA) is a life-threatening disease process involving numerous pathophysiologic changes that can be markedly exaggerated in the pregnant state.[1] This acute metabolic disorder may be the first manifestation of undiagnosed diabetes mellitus, or it may be the result of inadequate insulin therapy in a known diabetic patient. Even though DKA is more common with type 1 diabetes it may be seen in patients with type 2 diabetes and gestational diabetes under conditions such as stress due to severe intercurrent illness or in pregnancy with the use of corticosteroids for fetal lung maturity and β_2-agonists for tocolysis.[2–4] An episode of DKA in pregnancy compromises both the mother and the fetus and may lead to fetal death.

The reported incidence of DKA outside of pregnancy ranges from 4.6 to 8 events per 1000 patients annually.[5] The overall prevalence of DKA during pregnancy and the fetal loss associated with has decreased significantly in recent years. Whereas previous reported incidence of DKA during pregnancy was 9.3%,[6] more recent retrospective studies[7,8] found an incidence of DKA in pregnancy of 1%–2%. This trend is likely due to prenatal counseling and improved understanding and management of the acute event. The occurrence of DKA in pregnancies complicated by gestational diabetes mellitus or type 2 diabetes is rare;[9] thus, when it is encountered, the possibility of unrecognized preexisting diabetes should be strongly considered.

The overall incidence of fetal and maternal mortality secondary to DKA in pregnancy is limited to data from case series. The incidence of maternal mortality is historically reported as 5%–15%.[10] As the overall incidence of DKA in pregnancy, the maternal mortality appears to be declining. More recent studies report maternal mortality rate to be less than 1%.[11] Fetal loss rate, however, is much higher. Unlike previous studies which reported a fetal mortality rate of 35%–85%,[11,12] a more recent studies[7,13] found a lower fetal loss rate of 9%–10%.

This chapter will address the pathophysiology, effect on the fetus, and management of DKA in pregnancy to offer data to improve maternal and fetal outcome.

Pathogenesis

DKA is a state of inadequate insulin (either absolute or relative lack), causing perceived hypoglycemia at the level of adipose, muscle, and liver tissue. In response to cellular hypoglycemia, insulin counterregulatory hormones such as glucagon, cortisol, and catecholamines are released into the circulation, causing gluconeogenesis and glycogenolysis at the level of the liver.[14,15]

Hyperglycemia

Hyperglycemia in DKA originates from three major sources: first, high levels of glucose precursors as glycerol and amino acids due to lipolysis and muscle breakdown respectively; second, enhanced breakdown of glycogen stores; and third, a decreased peripheral uptake of glucose, caused by inadequate insulin and increased counterregulatory hormones.

High levels of glucose within the circulation result in an osmotic diuresis, leading to profound hypovolemia and dehydration, which further exacerbate the acidosis. The ensuing hypovolemia, in turn, further stimulates the release of other counterregulatory stress hormones such as catecholamines, growth hormone, and cortisol while enhancing the release of glucagon and thereby, escalates tissue insulin resistance.[16,17]

Acidosis

Increase in minute ventilation at the alveolar level places the gravid woman in a state of respiratory alkalosis. This is compensated by increased excretion of bicarbonate at the renal level. This state of "compensated respiratory alkalosis" during pregnancy plays its role by decreasing the pregnant woman's capability of buffering acids present during episodes of DKA.

Plasma ketone bodies are strong organic acids that dissociate at physiological pH to generate hydrogen ions. In DKA, rapid rise in plasma hydrogen-ion concentration outstrip the buffering capacity of the body, leading to decreased pH and metabolic acidosis. Acidosis is further exacerbated by the decrease in bicarbonate levels owing to bicarbonate neutralization of the ketone bodies prior to their excretion in urine. As a result, a compensatory metabolic acidosis is added to the baseline relative respiratory alkalosis and metabolic acidemia of pregnancy. Thus, already diminished buffering capacity of pregnancy is compounded by the reduction of ketones and severe impairment in bicarbonate regeneration. Severe acidosis has a negative inotropic effect on cardiac muscle,[18] exacerbates systemic hypotension by inducing peripheral vasodilatation and may cause respiratory depression,[19] central nervous system (CNS) depression, and insulin resistance.[20]

Ketogenesis

Profound hypoinsulinemia and excesses of the catabolic hormones, particularly the catecholamines, promote lypolysis, leading to high amounts of free fatty acids (FFA) in the circulation. FFA is the principal substrate for hepatic ketogenesis, which is enhanced by the increased portal delivery of fatty acids. In DKA, hepatic reesterification is impaired and α-oxidation of these FFA leads to the formation of ketone bodies, namely α-hydroxybutyrate and acetoacetate,[21] concomitant with a decrease in ketone used by muscle.[22] The increased levels of ketone bodies, combined with lactic acid from peripheral hypoperfusion, result in the metabolic acidosis seen with DKA.

Fluid and Electrolyte Depletion

The hyperglycemia causes osmotic diuresis when the renal threshold for glucose is exceeded, leading to depletion of intravascular volume, dehydration, and secondary losses of electrolytes.[23] The increase in plasma osmolarity leads to secondary intracellular dehydration. Contraction of the extracellular fluid volume causes a reduction in renal blood flow, which impairs the kidney's ability to clear glucose and ketone bodies. In advanced DKA, all body compartments become dehydrated, with a significant depletion in water, sodium, potassium, chloride, magnesium, phosphate, and bicarbonate. Shock secondary to the depleted intravascular volume may ensue, with decreased tissue perfusion and increased lactic acid production.

Sodium

Urinary sodium losses are exacerbated by severe hyperglycemia and insulin deficiency. In DKA, insulin deficiency per se may also contribute to renal losses of water and electrolytes because insulin stimulates salt and water reabsorption in the proximal and distal nephron. In DKA, there may be also "pseudohyponatremia" that is secondary to the hyperglycemic and hypertriglyceridemic state; this may be corrected by increasing measured sodium by 1.6 mEq/L for each 100 mg/dL of glucose above 100 mg/dL.[16]

Potassium

Metabolic acidosis leads to increased entry of hydrogen ions into cells, displacing intracellular potassium ions, which are also lost in urine or vomit. Although total body potassium may be considerably depleted, plasma potassium levels at presentation are usually normal or even high due to acidosis, insulin deficiency, and renal impairment.[24]

Phosphate

Total body phosphate deficiency is a characteristic feature of DKA. Phosphate deficiency is associated with reduced red cell 2,3-diphosphoglycerate levels, with impaired release of oxygen from oxyhemoglobin resulting in reduced oxygen delivery to the tissues.[25]

Increased Risk of DKA in Pregnancy

In pregnant women with diabetes, DKA usually occurs in the second and third trimesters (80%–90% of presentations) due to increased insulin resistance; however, DKA may occur at any time during pregnancy especially in newly onset of type 1 diabetes.[7,26] DKA is a major clinical problem in pregnancy as it tends to occur at lower blood glucose levels and more rapidly than in nonpregnant patients.[27,28] Precipitating factors include emesis, infections, omission of insulin during an acute illness, insulin pump failure, noncompliance, failure to diagnose new onset of diabetes, drug and alcohol use, and medications such as steroids and adrenergic agonists. Noteworthy, treatment with short-acting insulin analogues during pregnancy share similar DKA rates in comparison to regular insulin,[29] however, continuous subcutaneous insulin infusion (CSII) was associated with an increased rate of DKA in comparison to multiple daily injections, mainly due to pump failure.[30]

FACTORS CONTRIBUTING TO INCREASED RISK OF DKA IN PREGNANCY

Insulin Resistance

Pregnancy is a state of insulin resistance relatively insulin-resistant state, and this insulin resistance increases throughout gestation.[31] Several hormones such as human placental lactogen

(HPL), cortisol, and prolactin are elevated during pregnancy and serve as a counterregulatory hormone for protection against the hypoglycemic state at the cellular level. In addition, the physiological rise in progesterone with pregnancy decreases gastrointestinal motility that contributes to increased carbohydrate absorption causing hyperglycemia.[32]

"Accelerated Starvation"

In the second and third trimesters of pregnancy, there is a relative state of "accelerated starvation." The fetus uses large amounts of maternal glucose as a major source of energy and this leads to decreased maternal fasting glucose, which in association with relative insulin deficiency, leads to increased FFA levels with conversion to ketones in the liver.[32] In addition, acid–base adaptations in pregnancy previously mentioned lead to a state of compensated respiratory alkalosis. Increase in renal excretion of bicarbonate leading to lower buffering capacity in the gravid state. Altering the ability to buffer ketoacids, makes the pregnant diabetic patient to be susceptible to develop DKA even at lower levels of hyperglycemia then those seen in nonpregnant patients.[33] Moreover, high levels of human chorionic gonadotropin have been associated with nausea and emesis, exacerbating the already hypoglycemic state of pregnancy. Dehydration from emesis results in increased release of stress hormones that have insulin antagonistic effects.[8] Thus, any event that may lead to stress at the physiologic level places a gravid diabetic patient at risk for the development of DKA.

CLINICAL PRESENTATION AND DIAGNOSIS

The appearance of DKA is usually gradual and develops progressively over a period of 2–5 days. Common symptoms include polyuria, polydypsia, blurred vision, anorexia, nausea, vomiting, and weight loss. Moreover, decreased perception of fetal movements and nonreassuring fetal heart rate tracing can be part of the clinical picture. Moreover, in cases of more acute presentations, Kussmaul's breathing and hyperventilation as an effort to compensate for the metabolic acidosis, signs of volume depletion, tachycardia, and hypovolemic shock can appear. Importantly, it should be remembered that during pregnancy, DKA can emerge with nonelevated serum glucose values.

A high index of suspicion and prompt diagnosis is the key to improved outcome of fetus and mother. The diagnosis is confirmed by laboratory documentation of potential and sometimes moderate hyperglycemia, acidosis and ketonuria. Ketonemia and prerenal azotemia with elevations in blood urea nitrogen and creatinine levels are also common findings. Arterial blood gas analysis reveal acidosis with pH usually below 7.30, along with an anion gap of 12 mEq/L or greater caused by unmeasured anions: ketoacids and lactic acid. Serum bicarbonate will often be ≦15 mEq/L. As described earlier, sodium and potassium levels can vary significantly.

Effect of DKA on the Fetus

The greatest hazard facing the pregnant diabetic patient with DKA is fetal loss. The exact fetal loss rate is difficult to assess because of the small reported series in the literature. Indeed, the reported perinatal mortality until 15–25 years ago was reported to be as high as 30%–90%.[12,26] However, remarkable progress has been made both in the in fetal assessment techniques and in the treatment of DKA that mortality rate in other reviews is about 9–10%.[7,13] Fetal loss is primarily related to the severity of the maternal illness and the degree of metabolic decompensation. Most fetal losses occur prior to diagnosis and onset of efficient treatment. As ketone bodies freely cross the placenta, maternal acidosis is assumed to cause fetal acidosis. However, the exact mechanism by which maternal DKA affects the fetus remains unclear. Suggested mechanisms include a decrease in uterine blood flow and maternal hyperketonemia which induces fetal hypoxemia. Fetal hyperglycemia by itself can cause an increase in fetal oxidative mechanism and decreased fetal myocardial contractility. Indeed, fetal potassium deficit has been found to lead to fetal cardiac arrest.[34] Fetal hypoxia may also be attributed to a DKA-associated phosphate deficit which leads to depletion of red cell 2,3-diphosphoglycerate and consequent impairment of oxygen delivery. The risk of fetal distress and even death during maternal DKA state makes it mandatory to continuously monitor the fetal heart, assess the biophysical score, and evaluate fetal acid base balance by cordocentesis if necessary.

In the few case reports of fetal monitoring during maternal DKA, a nonreassuring pattern with tachycardia, reduced variability, and late decelerations was reported.[35,36] It was suggested that the administration of sodium bicarbonate alone for two hours led to the resolution of the late decelerations, decreased variability, and uterine contractions.[37] Additionally, others[36] reported the resolution of a similar fetal heart rate pattern 40 minutes after intravenous administration of insulin with no mention of maternal rehydration. Other researchers reported that a combination of massive intravenous hydration, insulin therapy, and intensive care of the mother lead to resolution of fetal acidosis and improved the fetal heart rate monitoring.

The long-term effects on surviving fetuses exposed to episodes of DKA in utero remain unclear. Several studies suggest an association between high levels of ketoacids during pregnancy and decreased cognitive and mental development scoring.[38,39]

Treatment

Initial assessment regarding diagnosis of DKA should be made promptly and an organized plan is set in motion to decrease the maternal and fetal mortality. This plan should involve a multidisciplinary team, which includes a perinatologist, an intensive care specialist, endocrinologist or general internist, and skilled obstetric and intensive care nursing support.

All treatment protocols are based on correcting volume depletion, supplying insulin, correcting acidosis and electrolyte imbalance, and importantly, ascertaining and correcting any precipitating factors that brought about the current episode of DKA. Continuous fetal heart rate monitoring and biophysical assessment are mandatory to assess fetal well-being, especially during the third trimester.

Resolution and treatment of DKA in the mother often results in correction of the fetal physiologic response to the disease process. Pregnancy itself does not alter the management of DKA. Recommendations for volume replacement, correction of hyperglycemia, and electrolyte disturbances are the same regardless of whether a person is pregnant.

Induction of labor or emergency cesarean section should be done only after maternal stabilization. In the event of preterm labor, β-mimetic drugs are relatively contraindicated as they may exacerbate the metabolic disorder and alter the delicate hemodynamic state. Major consideration should be given to steroid use for lung maturation from the same metabolic consequences. The physician should have concern and anticipation for the onset of DKA or worsening of its course and act accordingly, however, this concern should not be a burden for treatment if it necessitate by the treating physician.

Several protocols have been suggested for the treatment of DKA. However, these protocols are only general guidelines and the therapeutic regimen is tailored to the individual patient on the basis of her prominent clinical features.

Monitoring

During DKA treatment in pregnancy, clinical and laboratory close monitoring is needed. Vital signs (pulse rate, blood pressure, respiratory rate, conscious status) have to be followed each hour. If consciousness is compromised, or in the presence of severe DKA (pH <7.1 or bicarbonate >5 mEq/L), admission to the intensive care unit has to be considered. If the patient cannot void, bladder catheterization is necessary to follow urine output adequately. Initially, serum glucose, electrolytes, blood urea nitrogen, creatinine, calcium, phosphate, and blood gases are obtained. Subsequently, blood glucose is measured bedside by a glucose reflectance monitor hourly, serum glucose and electrolytes every two hours, and blood gases every four hours.

A flow sheet tabulating these findings as well as, insulin dose, fluid and electrolyte administration, and urine output allows easy follow-up of response to therapy.

Fluid and electrolyte depletion

An estimated dehydration of 5%–10% occurs in DKA adult patients (estimation of 4–10 L of deficit).[40] As estimating fluid deficit may be challenging, it was recommend calculating 100 mL/kg of body weight when determining overall fluid deficit.[41] Adequate rehydration is considered the first priority of treatment to improve renal perfusion and thereby, increasing glucosuria to improve tissue perfusion.[42]

The initial therapy should be based on isotonic saline for effective restoration of the intravascular volume. Because of the hyperglycemia, hyperosmolarity is universal in DKA; thus even NaCl 0.9% is hypotonic relative to the patient's serum osmolarity. A gradual decline in osmolarity is desirable because a too rapid decline has been implicated in the development of cerebral edema.[43]

Importantly, it has been postulated that using hypotonic saline as initial treatment may cause a rapid drop in plasma osmolarity that can lead to fatal cerebral edema. Isotonic normal saline should be administered as 1000–2000 mL/h for the first 1–2 hours. This aggressive administration immediately increases tissue perfusion by increasing the markedly depleted intravascular volume. In addition, glucose values are decreased through hemodilution and through increased renal loss of glucose when renal perfusion is improved. After the first 1–2 hours, fluids are administered at a rate of 250–500 mL/h, with a long-term goal of correcting 75% of fluid deficit over a 24-hour period.[41]

As a rapid volume overload has also been implicated in the etiology of cerebral edema, the fluid replacement after the first hour is provided according to the sum of the maintenance amount of fluid (1.5 L/m²/d) plus one half of the fluid deficit over the first 24 hours and the remainder over the subsequent 24 hours. In the presence of persistent hyperglycemia and negative fluid balance, it may be worthwhile adding the amount of urine to the calculation of the fluids. When serum glucose falls below 250 mg/dL, the intravenous fluids are changed to 5% dextrose solution with NaCl 0.45%. Yet, in the presence of hyponatremia it is suggested to continue with 5% dextrose solution with NaCl 0.9%. If serum glucose falls below 150 mg/dL, 10% dextrose solution is added to the infusate. This management continues the process of restoring the glucose supply to the tissues, which has been reduced under conditions of insulin deficiency.

Potassium

Potassium stores are depleted in DKA (estimated deficit 3–5 mEq/kg) keeping in mind that the often normal or elevated serum potassium level may not reflect the true total deficit.[44] Still, hypokalemia can ensue during treatment with insulin and fluids. Insulin-mediated potassium transport into cells, resolution of the acidosis (which also promotes potassium entry into cells), and urinary loss of potassium salts of organic acids can develop or exacerbate hypokalemia. Thus, potassium repletion should commence as soon as adequate urine output and normal serum potassium are documented. Potassium repletion should be delayed until the potassium falls into the normal range. Inclusion of 20–40 mEq of potassium in each liter of IV fluid is reasonable; however, additional potassium supplements may also be required. If potassium level is below 5.5 mEq/L, KCl 40 mEq/L is administrated, and if potassium level is below 4 mEq/L, KCl 60 mEq/L is administrated. Potassium phosphate or acetate can be substituted for the chloride salt to reduce the amount of chloride administered. The goal is to maintain the serum potassium >3.5 mEq/L (3.5 mmol/L). If the initial serum potassium is <3.3 mEq/L, insulin should not be administered until the potassium is supplemented to >3.3 mEq/L.[45]

Phosphate

No well-documented clinical significance of phosphate depletion has been determined and no benefit of phosphate administration has been demonstrated.[46] However, if phosphorus is low (phosphorus <1.0 mg/dL) and is associated with muscular weakness or respiratory depression, replacement of a third of the potassium amount should be given as potassium phosphate. There needs to be vigilance in monitoring for its possible complications as hypocalcemia and hypomagnesemia.

Insulin

The objective of insulin treatment in DKA is to arrest further metabolic decompensation, inhibit lipolysis and thus ketogenesis, inhibit hepatic glucose production and enhance uptake of glucose and ketone bodies into the peripheral tissues. In DKA, if patients are under CSII treatment, the insulin pump should be disconnected during the acute phase of treatment. Insulin is best given intravenously because it assures rapid distribution and

allows adjustment of the infusion rate as the patient responds to therapy. Insulin is diluted in isotonic saline (with 50 units in 500 mL saline 0.9%, the insulin concentration is 1 unit/10 mL). Short-acting insulin (i.e., Regular insulin) should be administered IV 0.1 unit/kg or IM 0.3 units/kg as a bolus followed by 0.1 unit/kg/h. This dosage should place the initial bolus and maintenance insulin level at about 10 units.

Intravenous regular insulin should be continued until the acidosis resolves and the patient is metabolically stable. As the acidosis and insulin resistance associated with DKA resolve, the insulin infusion rate can be decreased (to 0.05–0.1 units/kg/h). Insulin infusion should be maintained at the same rate as long as acidosis persists, even when normal glucose levels have been achieved. Even relatively brief periods of inadequate insulin administration in this transition phase may result in DKA relapse.

Hyperglycemia usually improves at a rate of 75–100 mg/dL/h as a result of insulin-mediated glucose disposal, reduced hepatic glucose release, and rehydration. If glucose levels do not fall by 50–75 mg/dL over the first hour, then the hourly infusion rate should be doubled. Ideally, serum glucose should not fall faster than 100 mg/dL/h. When the plasma glucose reaches 250 mg/dL, 5% dextrose solution should be added to the 0.45% saline infusion to maintain the plasma glucose in the 150–250 mg/dL range,[40] and the insulin infusion should be continued. Ketoacidosis begins to resolve as insulin reduces lipolysis, increases peripheral usage of ketone bodies, suppresses hepatic ketone body formation, and promotes bicarbonate regeneration. However, hyperglycemia resolves faster than acidosis and ketosis. As ketoacidosis improves, β-hydroxybutyrate is converted to acetoacetate, thereby paradoxically ketone body levels may appear to increase if measured by laboratory assays only detects acetoacetate and acetone. The improvement in acidosis and anion gap, a result of bicarbonate regeneration and decline in ketone bodies, is reflected by a rise in the serum bicarbonate level and the arterial pH. A hyperchloremic acidosis often follows successful treatment and gradually resolves as the kidneys regenerate bicarbonate and excretes chloride.

After acidosis has been corrected and the patient is able to eat, subcutaneous insulin (neutral protamine Hagedorn [NPH] and Regular or Regular alone) is administrated and patients that were previously on pump therapy can continue its use. Insulin and

Management of Diabetic Ketoacidosis

1. Admit to hospital: intensive care setting may be necessary for frequent monitoring.
2. Involve a multidisciplinary team: perinatologist, intensive care specialist, endocrinologist, or general internist.
3. Assess:
   - Serum electrolytes (K^+, Na^+, Mg^{2+}, Cl^-, phosphate)
   - Acid–base status: pH, HCO^{3-}, PCO^2, β-hydroxybutyrate
   - Renal function (creatinine, urine output)
   - Fetal status: non-stess test (NST), bio-physical profile BPP (in 2nd and 3rd trimesters)
4. Replace fluids:
   - 1–2 L of 0.9% saline over first 1–2 hours (10–15 mL/kg/h)
   - Subsequently (unless hyponatremia) change to 0.45% saline at 150–300 mL/h.
   - When plasma glucose reaches 250 mg/dL: 5% glucose and 0.45% saline at 100–200 mL/h and decrease insulin infusion rate 0.05–0.1 unit/kg/h to maintain glucose between 150 and 250 mg/dL.
5. Administer short-acting insulin:
   - IV 0.1 units/kg as a bolus and then IV 0.1 units/kg/h; increase two- to threefold if no response by 2–4 hours.
   - Do not administer insulin until the potassium is corrected to >3.3 mEq/L.
6. Assess precipitating factors:
   - Possible etiologies: emesis, infections, pumps failure, noncompliance, new onset of diabetes, drugs, alcohol use or medications (steroids and adrenergic agonists).
   - Initiate appropriate workup for precipitating event (cultures, chest X-ray, ECG).
7. Meticulous serial monitoring:
   - Blood pressure, pulse, respirations, mental status, fluid intake, and output every 1–4 hours.
   - Capillary glucose every 1–2 hours.
   - Electrolytes (especially K^+, bicarbonate, phosphate) and anion gap every four hours for first 24 hours.
   - Fetal status
8. Replace K^+:
   - 40 mEq/L when plasma K^+ <5.5 mEq/L, ECG normal, urine flow and normal creatinine documented.
   - 60 mEq/L when plasma K^+ <3.5 mEq/L or if bicarbonate is given.
9. Replace phosphate:
   - If phosphate <1.0 mg/dL and is associated with muscular weakness/respiratory depression give potassium as 2/3 KCl and 1/3 KPO4.
10. Assess need for Bicarbonate:
    - If pH = 6.9–7.0: 50 mEq/L of sodium bicarbonate in 200 mL of sterile water with 10 mEq/L KCl over one hour.
    - If pH <6.9: 100 mEq/L of sodium bicarbonate in 400 mL of sterile water with 20 mEq/L KCl over two hours.
    - Repeat the dose of bicarbonate every two hours until the arterial pH is >7.0.
11. Continue all above until patient is stable, glucose goal is 150–250 mg/dL, and acidosis is resolved.
12. Administer intermediate or long-acting insulin as soon as patient resumes eating. Allow 30 minutes overlap in insulin infusion and subcutaneous insulin injection.

fluid infusion is discontinued only 30 minutes after the subcutaneous insulin injection.

Bicarbonate

The use of bicarbonate is the most controversial component in the treatment of DKA.[37,40] Routine bicarbonate therapy may be unnecessary, as the retained ketone bodies are metabolized and regenerated to bicarbonate. Bicarbonate therapy is indicated only in patients with severe acidosis (pH <7.0 or bicarbonate <5 mEq/L after initial hydration). When administrated, 50 mEq/L of sodium bicarbonate in 200 mL of sterile water with 10 mEq/L KCl over 1 hour if pH = 6.9–7.0; or 100 mEq/L of sodium bicarbonate in 400 mL of sterile water with 20 mEq/L KCl over 2 hours if pH <6.9. Doses of bicarbonate should be repeated every two hours until the arterial pH is >7.0. Importantly, alkali therapy is associated with many side effects. Overzealous replacement should be avoided because rapid reversal of maternal acidosis may impair cardiac function, reduce tissue oxygenation, and promote hypokalemia.[34] Additional CNS depression may result from paradoxical reduction of the brain pH as the systemic acidosis is rapidly corrected.

SUMMARY

Episodes of DKA and especially severe ones with loss of consciousness are rare, particularly in the gravid state. However, when present, DKA can represent a life-threatening emergency both for mother and fetus. The majority of DKA cases occur in patients who have pregestational diabetes either known or not. Pregnancy per se places the gravid diabetic patient at an enhanced risk for development of DKA. A high index of suspicion and prompt diagnosis is the key to improved outcome of mother and fetus. The diagnosis is confirmed by the hallmark laboratory findings of hyperglycemia, acidosis, and ketonuria. Treatment involves aggressive fluid management, insulin administration, and identification and treatment of precipitating causes. If patients are under CSII treatment, the insulin pump should be disconnected during the acute phase of treatment, prompt care should be taken to stabilize and treat the mother as a first priority as most fetal heart rate abnormalities subside after correction of maternal hypovolemia and acidosis.

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Confronting Hypoglycemia in the Pregnant Diabetic

33

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The mother of excess is not joy – but joylessness

—Nietzsche

Key Points

- Hypoglycemia is a common complication of insulin therapy in people with diabetes.
- Type 1 diabetes may cause hypoglycemia unawareness that may lead to neuroglycopenia, seizures, coma, injury, and death.
- Pregnancy diminishes the counterregulatory responses to hypoglycemia.
- The incidence of hypoglycemia in women with type 1 diabetes increases during pregnancy, particularly during the first half of pregnancy.
- Animal studies demonstrate that hypoglycemia during critical periods of embryogenesis may affect embryonic development and survival.
- Maternal hypoglycemia does not appear to have adverse effects on the developing human fetus.
- Meticulous self-monitoring of blood glucose and measured corrections of abnormal levels are the key to avoiding extreme fluctuations of glycemic control.

INTRODUCTION

Hyperglycemia is well known to have adverse effects on the outcome of pregnancy in women with diabetes. Therefore, the primary focus in the management of pregnant women with diabetes is on maintaining normoglycemia throughout pregnancy. Women with pregestational diabetes (either type 1 or type 2) often receive during pregnancy the most intensive insulin therapy they have ever experienced, and concern for the well-being of their offspring will often motivate them to be receptive to this mode of therapy. Obstetricians providing prenatal care for women with pregestational diabetes usually set targets of glycemic control that are considerably stricter than those for nonpregnant diabetics. Consequently, hypoglycemic episodes are quite common in these patients, primarily in those that have type 1diabetes and predominantly during the first half of pregnancy. When severe, these episodes of hypoglycemia may result in significant maternal morbidity, or even mortality. Women with long-standing type 2 diabetes who have diminished endogenous production of insulin and who are dependent on exogenous insulin or certain oral hypoglycemic agents are also at risk for hypoglycemia, although the incidence and severity of hypoglycemia in this population is lower. Even women with gestational diabetes who are treated with insulin or with oral hypoglycemic agents are at risk for hypoglycemia, but the risk in this population is considerably smaller than in those with pregestational diabetes. In caring for pregnant women with pregestational diabetes, particularly those with type 1diabetes, the potentially life-threatening risk of hypoglycemia is often downplayed, or even overlooked, in the unrelenting pursuit of normoglycemia.

HYPOGLYCEMIA IN THE NONPREGNANT DIABETIC

In type 1 diabetes, the pancreas is unable to secrete insulin and to modify its concentration in accordance with the concentration of glucose in the blood (i.e., decrease insulin secretion in the face of declining blood glucose concentrations). All insulin in these patients is delivered from an exogenous source, and often there is too much insulin relative to the prevailing blood glucose concentration, and hypoglycemia ensues. Indeed, hypoglycemia is the most common side effect in patients with type 1 diabetes receiving intensive insulin therapy, and it is also their greatest fear.

Iatrogenic hypoglycemia is defined as an abnormally low plasma glucose concentration that exposes the individual to potential harm.[1] The threshold glucose concentration associated with symptomatic hypoglycemia varies among individual patients, such that a single value cannot be assigned for all patients. The American Diabetes Association and The Endocrine Society have suggested that a glucose concentration of 70 mg/dL or less should alert to the possibility of developing symptomatic hypoglycemia.[1] Symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are associated with a low glucose

concentration. Severe symptomatic hypoglycemia is an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions. Patients with type 1 diabetes who are treated with conventional therapy experience an average of one symptomatic hypoglycemic episode a week, whereas intensive insulin therapy is associated with two symptomatic episodes a week.[2] Estimates on the frequency of severe hypoglycemia among nonpregnant individuals with type 1 diabetes range from 115 to 320 episodes per 100 patient-years, and from 35 to 70 per 100 patient-years among those with type 2 diabetes.[3,4] Such episodes include the need for glucagon or intravenous glucose administration, emergency room treatment, seizures, loss of consciousness, coma, or even death. In fact, current estimates attribute 4%–10% of all deaths in patients with type 1 diabetes to hypoglycemia.[5–8]

Much of the variation in the reported incidence of hypoglycemia stems from lack of uniformity with respect to the definition of hypoglycemia. The threshold of biochemical hypoglycemia (a measured low blood glucose concentration without consideration of presence or absence of symptoms) has variably been set between 45 and 70 mg/dL glucose in plasma. The term "symptomatic hypoglycemia" encompasses those symptoms that are commonly associated with low blood glucose concentrations and includes the symptoms of neuroglycopenia (altered sensation, inability to concentrate, disorientation, seizures, coma) and the symptoms associated with activation of the sympathetic system (tremor, palpitations, perspiration, agitation). However, these symptoms lack specificity and they do not correlate well with glucose concentrations.[9] Apparently, several additional factors besides the actual glucose concentration contribute to the presence or absence of symptoms, such as antecedent episodes of hypoglycemia, the prevailing level of glycemic control, the duration of diabetes, the rate of decline in the glucose concentration, and individual variation.

NORMAL COUNTERREGULATORY PHYSIOLOGY

The central nervous system is dependent on glucose as its primary source of energy. Because the brain can neither synthesize glucose nor store more than minute amounts of glycogen, it is critically dependent on continuous delivery of glucose in the circulation to maintain its function. Hypoglycemia results in neuroglycopenia, which is manifested clinically as altered mentation and may progress to seizures, coma, and even death.

The intact body has redundant protective mechanisms to prevent hypoglycemia. These counterregulatory hormonal responses include the secretion of glucagon and epinephrine that act within minutes to maintain euglycemia, and the secretion of growth hormone and cortisol that have a prolonged action lasting several hours. These mechanisms are invoked in the presence of insulin-induced hypoglycemia, late after glucose ingestion, and during exercise. During insulin-induced hypoglycemia in normal subjects, secretion of counterregulatory hormones and recovery from hypoglycemia occur within minutes. Glucagon and epinephrine can each act independently to counteract the hypoglycemic insult, by triggering breakdown of glycogen stores in the liver (glycogenolysis) and synthesis of glucose from precursors (gluconeogenesis). Glucagon may also act by limiting peripheral utilization of glucose. Moreover, activation of the autonomic system causes hypoglycemia awareness, characterized by irritability, anxiety, tremor, sweating, and palpitations. Hypoglycemia awareness promotes caloric intake and thus contributes further to counteract the hypoglycemic episode.

Glycemic thresholds for activation of the counterregulatory mechanisms, as well as thresholds for hypoglycemia awareness and altered mentation, are subject to individual variability. In general, secretion of epinephrine and glucagon in normal subjects begins at glucose concentrations of 64–68 mg/dL in arterialized venous plasma; autonomic symptoms begin at 56–60 mg/dL, and symptoms of neuroglycopenia begin at 48–54 mg/dL (Figure 33-1).[10,11] Thus, the human body has a cascade of responses to progressive hypoglycemia which maximizes the opportunity to prevent, as well as correct, its deleterious effects.

IMPAIRED GLUCOSE COUNTERREGULATION IN DIABETES

Insulin-dependent diabetes is associated with defective glucose counterregulation and hypoglycemia unawareness. Impairment of glucagon secretion from the pancreatic islet alpha cells usually occurs within five years of onset of type 1 diabetes,[12] although the mechanisms underlying this deficiency are unknown. Many patients with type 1 diabetes, particularly those with long-standing disease of 10 years or more, also manifest a deficient counterregulatory epinephrine response to hypoglycemia. Several investigators have shown that in subjects with type 1 diabetes, secretion of epinephrine in response to falling blood glucose concentrations is both delayed (occurs at lower glucose concentrations) and diminished (lower peak epinephrine responses) compared to normal controls.[13–15] Defective epinephrine secretion in response to hypoglycemia in these subjects is associated with hypoglycemia unawareness, namely the lack of perceived autonomic responses to hypoglycemia (palpitations, tremor, sweating, etc.). Consequently, many subjects fail to recognize the impending dangers of the falling blood glucose concentration and do not react to prevent the progression to neuroglycopenia. Once in the

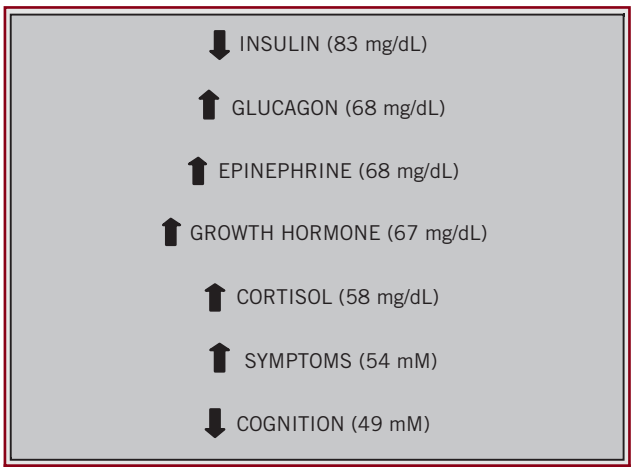

Figure 33-1 Thresholds of plasma glucose concentrations for activation of normal counterregulatory responses to hypoglycemia. (Adapted from P. Cryer[13])

altered mental state associated with neuroglycopenia, the ability to recognize the dangerous situation and to take action becomes increasingly difficult, and the patient may deteriorate to a state of seizures, coma, or even death.[16] Defective glucose counterregulation and hypoglycemia unawareness are components of hypoglycemia-associated autonomic failure (HAAF), a form of sympatho-adrenal failure that should be distinguished from classic diabetes-associated autonomic neuropathy. A major contribution to the development of HAAF is recent antecedent iatrogenic hypoglycemia[17] and avoidance of hypoglycemia may contribute to reversing that process.

The pathophysiology of deficient autonomic counterregulation and hypoglycemia unawareness in type 1 diabetes is not clear. This autonomic failure is distinct from classic diabetic peripheral and autonomic neuropathy which involves loss of nerve fiber. It is possible that the defective counterregulatory response to hypoglycemia in type 1 diabetes is related to a cerebral defect in the hypothalamus, where the counterregulatory response is thought to be initiated and regulated.[18] Indeed, the decreased pituitary responses to hypoglycemia (decreased adrenocorticotropic hormone [ACTH], growth hormone, and prolactin responses) found in subjects with type 1 diabetes[19] may point to the role of the central nervous system in the syndrome of defective counterregulation. Another factor that may have a role in hypoglycemia unawareness is the level of angiotensin-converting enzyme (ACE) activity. Low levels of ACE activity have been associated with lower frequency of severe hypoglycemia, whereas subjects with high levels of ACE activity are more prone to severe hypoglycemia and more susceptible to cognitive impairment during hypoglycemia.[20–22]

In addition to defects in counterregulation that occur as a result of the disease process in type 1 diabetes, there is evidence suggesting that institution of intensive insulin therapy to achieve euglycemia may alter the counterregulatory response to hypoglycemia. Simonson et al.[23] showed that release of epinephrine, growth hormone and cortisol in response to hypoglycemia were significantly reduced in patients with type 1 diabetes following 4–8 months of insulin pump therapy, compared to their responses prior to therapy. Indeed, patients with well-controlled type 1diabetes often tolerate subnormal plasma glucose concentrations without any symptoms of hypoglycemia. In such patients, a lower glucose concentration may be required to elicit symptoms and hormonal counterregulatory responses compared to patients who are less strictly controlled.[24,25] Furthermore, episodes of hypoglycemia compound the problem by further lowering glycemic thresholds for autonomic and symptomatic responses to subsequent episodes of hypoglycemia;[26,27] in other words, progressively lower glucose concentrations are required for activation of responses, following recurrent episodes of hypoglycemia. Whether the altered thresholds for activation of counterregulatory responses are also associated with altered thresholds for impairment of cognitive functions, is still a matter of debate.[16,28,29]

Thus, a vicious cycle of iatrogenic hypoglycemia is set into motion in patients with type 1 diabetes placed on intensive insulin therapy[16] (Figure 33-2): strict glycemic control predisposes to hypoglycemia, which is most severe in patients with compromised counterregulatory responses and hypoglycemia unawareness. Intensive insulin therapy further compromises counterregulatory responses, and increases the risk of hypoglycemia. The resulting recurrent episodes of hypoglycemia compromise counterregulatory responses even further, thereby setting into motion a vicious cycle.

Indeed, findings from the diabetes control and complications trial (DCCT) indicate that the substantially lower level of glycemia achieved with intensive insulin therapy compared to conventional therapy was accompanied by more than a threefold higher rate of severe hypoglycemia.[30] A third of these episodes were associated with seizure or coma, 20% resulted in emergency room treatment or hospitalization, and 1.5% of all severe hypoglycemia events resulted in motor vehicle accidents. In all, 70% of episodes occurred during sleep or without apparent warning symptoms. In this study, the risk of severe hypoglycemia was related to both the magnitude of decline in glycohemoglobin A1c and to the absolute level achieved. However, multivariate analyses that included demographic and disease-related variables failed to yield sensitive models for prediction of hypoglycemia.

INCIDENCE OF HYPOGLYCEMIA DURING PREGNANCY

Several investigators have reported high rates of moderate and severe hypoglycemia in pregnant women with type 1 diabetes treated with intensive insulin therapy. Rayburn[31] reported that 36% of pregnant women with type 1diabetes had severe hypoglycemia during pregnancy, with the peak incidence occurring during sleep between midnight and 8:00 am. Similar results were reported by Coustan[32] and Steel.[33] In Kimmerle's[34] sample population of 77 women with type 1 diabetes, a total of 94 episodes of severe hypoglycemia occurred in 35 of the 85 pregnancies (41%). The majority of these episodes occurred during the first half of pregnancy (84%) and during sleep (77%).

Hellmuth studied overnight hourly glucose concentrations in 43 women with type 1 diabetes during the first trimester of pregnancy.[35] Sixteen (37%) patients had at least one episode of biochemical hypoglycemia (venous whole blood glucose <55 mg/dL) during the night, and only one of these was symptomatic. A blood

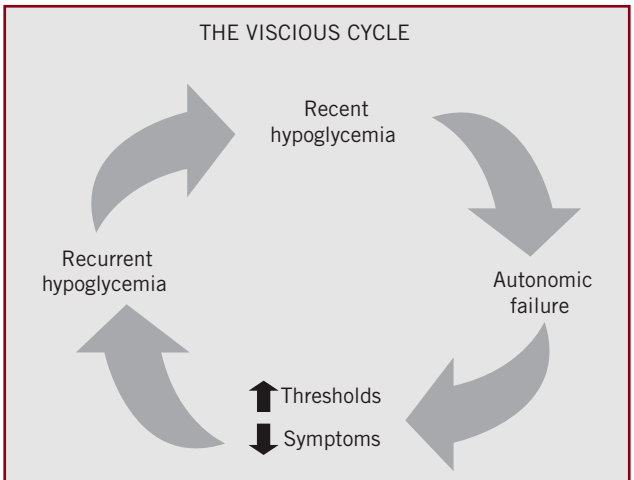

Figure 33-2 The vicious cycle. (Adapted from P. Cryer.[13])

glucose <118 mg/dL at 23.00 hours was associated with a 71% risk of nocturnal hypoglycemia.

More recently, Evers et al.[36] compared the incidence of severe hypoglycemia during the first trimester (before 17 weeks) to the incidence during the four months immediately preceding pregnancy among 278 women with type 1 diabetes. There was a threefold increase in the mean number of severe hypoglycemia episodes (from 0.9 to 2.6), and the proportion of women affected by severe hypoglycemia rose from 25% to 41%. Severe hypoglycemia was associated with a history of severe hypoglycemia prior to pregnancy, longer duration of diabetes, a lower HbA1c, and a higher total daily insulin dose. The same authors subsequently reported the incidence of severe hypoglycemia in a nationwide study in the Netherlands encompassing 323 women with type 1 diabetes.[37] They found that 41% of women had severe hypoglycemia during the first trimester and 17% during the third trimester. There was one maternal death following cardiac arrest attributed to severe hypoglycemia at 17 weeks gestation.

Nielsen et al.[38] conducted a prospective observational study of 108 pregnant women with type 1 diabetes, recording self-monitored plasma glucose values eight times a day for three days each time at 8, 14, 21, 27, and 33 weeks of gestation. Subjects completed a questionnaire on nausea, vomiting, hypoglycemia awareness, and history of mild and severe hypoglycemia. The incidence of mild hypoglycemia was 5.5 events per patient-week in early pregnancy and decreased throughout pregnancy. Forty-five percent of women experienced 178 episodes of severe hypoglycemia, corresponding to 5.3, 2.4, and 0.5 events per patient-year in the first, second, and third trimesters, respectively. The vast majority (80%) of severe hypoglycemic episodes occurred before 20 weeks, peaking at nine weeks gestation. Among the 34 women who experienced more than one episode of severe hypoglycemia, 11 women had five or more recurring episodes, accounting for 60% of all episodes. A history of severe hypoglycemia during the year preceding pregnancy and impaired hypoglycemia awareness were found to be independent predictors for severe hypoglycemia.

In our own study population of 84 pregnant women with type 1 diabetes followed prospectively within the framework of a clinical trial,[39] 79% had at least one recorded capillary blood glucose concentration of 35 mg/dL or less, and 27% had more than 10 such episodes during pregnancy. Furthermore, 33% of women had at least one episode of severe, symptomatic hypoglycemia resulting in seizure, coma, injury, or need for intravenous administration of glucose. Seven women were involved in motor vehicle accidents associated with severe hypoglycemia. Sixty-seven percent of the women had at least one episode of hypoglycemia requiring the assistance of another individual for recovery. The majority of symptomatic hypoglycemic episodes occurred during the first half of pregnancy, with the peak incidence between 8 and 13 weeks' gestation. Furthermore, a third of the patients had at least three episodes of severe biochemical hypoglycemia (recorded capillary blood glucose <35 mg/dL) during every two-week period of the first trimester (up to 17 weeks). It is very likely that the true incidence of biochemical hypoglycemia in this study population was much higher since not all such episodes were necessarily recorded by the patients. Conversely, the reported incidence of symptomatic hypoglycemia most likely reflects the true incidence of this complication; patients in this prospective study were seen every two weeks during pregnancy and were specifically queried during each visit on the details of any symptomatic hypoglycemic episodes that might have occurred since the previous visit, thus minimizing recall bias.

The advent of continuous glucose monitoring with a subcutaneous sensor that measures interstitial glucose concentrations every few minutes has allowed a more valid and comprehensive assessment of the 24-hour glucose profile compared to self-glucose monitoring performed several times a day. It also allows monitoring of nocturnal glucose levels as well as changes that precede hypoglycemia. Continuous glucose monitoring has demonstrated that over each 24-hour period, pregnant women with type 1 diabetes spend 3.5 hours in the hypoglycemic range of <70 mg/dL, and 1.4 hours at <50 mg/dL. At night, from 10 PM to 6 AM, glucose is <50 mg/dL during 0.6 hours. The duration of time spent in the hypoglycemic range decreases somewhat as pregnancy progresses. Interestingly, pregnant women with type 2 diabetes have similar durations of hypoglycemia during the night, but less so during other times of the day.[40]

Although hypoglycemia is primarily a matter of concern in pregnant women with pregestational diabetes treated with insulin, particularly those with type 1diabetes, recent data suggest that asymptomatic hypoglycemia is very common even among women with gestational diabetes treated with either insulin or glyburide. Yogev et al.[41] monitored interstitial glucose concentrations in 82 pregnant women with gestational diabetes and 35 nondiabetic controls. Using a continuous glucose monitoring system for 72 hours, they found that asymptomatic hypoglycemia (glucose concentration <50 mg/dL) occurred in 19 of 30 insulin-treated women (63%) and in 7 of 35 patients treated with glyburide (28%) but in none of the diet-treated or nondiabetic women. The mean number of recorded hypoglycemic episodes per day was twice as high in the insulin-treated women (4.2/day) than in the glyburide-treated women (2.1/day). Hypoglycemic episodes were primarily nocturnal (84%) in the insulin-treated women but were evenly distributed during the day and night among the glyburide-treated women.

Brustman et al.[42] reported on the incidence of hypoglycemia in 674 women with gestational diabetes who were treated with glyburide. Although two-thirds of the women had no documented blood glucose values in the hypoglycemic range (<50 mg/dL), one-third had 1%–7% of all their recorded glucose values <50 mg/dL. None of these women reported severe symptomatic hypoglycemia, although this information was not systematically sought in each follow-up visit. The incidence of asymptomatic hypoglycemia was associated with overall mean blood glucose, but not with the glyburide dose.

ETIOLOGY OF HYPOGLYCEMIA DURING PREGNANCY

It is not entirely clear why hypoglycemia occurs with such increased frequency in early pregnancy in women with type 1 diabetes compared to the nonpregnant state. As most patients with diabetes conceive without attaining strict glycemic control preconceptionally, the phenomenon may be related to the rapid institution of intensive insulin therapy once pregnancy has been

diagnosed. As mentioned previously, such therapy results in diminished counterregulatory hormonal responses to hypoglycemia[23] and an increased risk of hypoglycemia unawareness.[16] Another possibility is that pregnancy itself independently increases the risk of hypoglycemia. This could be related to hormonal changes of pregnancy as well as to the effects of pregnancy on the gastrointestinal system. The nausea and vomiting of pregnancy and delayed emptying of the stomach may both increase the likelihood of an insulin overdose, particularly during the first trimester. However, one study found no association between hypoglycemia and severe nausea and vomiting during pregnancy.[43]

The effects of pregnancy on the counterregulatory hormonal responses to hypoglycemia have been studied both in animals and in humans. Connoly et al.[44] studied counterregulatory responses in pregnant and nonpregnant dogs and found that pregnancy was associated with significantly diminished responses of glucagon and norepinephrine to hypoglycemia and markedly diminished net hepatic glucose output when compared to the nonpregnant state. Diamond et al.[45] induced hypoglycemia (plasma glucose concentration 44 mg/dL) in nine pregnant women with type 1 diabetes during the third trimester using the hypoglycemic clamp technique. Hypoglycemia failed to elicit a counterregulatory glucagon response and the epinephrine response was suppressed compared to historical data in nonpregnant subjects. Moreover, the plasma glucose level that elicited an epinephrine and growth hormone response was 5–10 mg/dL lower than in the nonpregnant state. We performed hypoglycemic clamp studies in a group of 17 women with type 1 diabetes and in 10 nondiabetic controls during which plasma glucose concentrations were decreased to 60 mg/dL.[46] Each subject underwent three studies: at 24–28 weeks gestation, at 32–34 weeks gestation, and at 12 weeks, or more, postpartum. This study design allowed each subject to serve as her own control in comparing counterregulatory responses during two stages in pregnancy and in the nonpregnant state, and to compare counterregulatory responses in women with diabetes to women without diabetes in pregnancy and postpartum. Women with diabetes had no detectable glucagon or cortisol responses to this level of hypoglycemia and the epinephrine response was significantly diminished compared to the nondiabetic controls. Additionally, the epinephrine response during pregnancy was significantly diminished compared to the nonpregnant state. In the nondiabetic controls, the counterregulatory glucagon response was diminished during pregnancy compared to the nonpregnant state. In both groups, the counterregulatory growth hormone response diminished progressively during pregnancy. Thus, there is ample data suggesting that diminished counterregulatory responses to hypoglycemia during pregnancy contribute to the increased incidence of hypoglycemia in pregnant women in general, and particularly in those with type 1 diabetes. It is also possible that pregnancy and intensive insulin therapy result in an additive effect that increases the risk of hypoglycemia in this population.

THE EFFECTS OF MATERNAL HYPOGLYCEMIA ON THE FETUS: ANIMAL MODELS

Several animal studies have demonstrated deleterious effects of hypoglycemia on embryonic development both in vivo and in vitro. Most studies have found that these effects depend on the timing and on the duration of hypoglycemia (Table 33-1). Thus, rat[47] and mouse[48] embryos cultured in hypoglycemic media for 24–48 hours demonstrated growth retardation and severe dysmorphic lesions. The effect of brief exposure to hypoglycemia (1–4 hours) appears to be dependent on the timing of the insult. When exposed to a brief (one hour) episode of hypoglycemia during an early and vulnerable period of embryogenesis, mouse[48] and rat[49] embryos had growth retardation and gross developmental anomalies. However, brief exposure to hypoglycemia at a later stage of development did not produce any abnormalities.[50] In other rat studies, brief maternal hypoglycemia was associated with skeletal malformations and delayed ossification in the fetuses, particularly in the fetuses of diabetic rats.[51] Smoak[52] has demonstrated a deleterious effect of hypoglycemia on the developing hearts of mouse embryos. Brief periods of hypoglycemia were associated with structural cardiac malformations, slowing of the heart rate, and increased glucose uptake and glycolysis by the heart. It appears

TABLE 33-1 Effects of Hypoglycemia on the Embryo: Animal Models

Author	Species	Timing of Hypoglycemia	Duration of Hypoglycemia (h)	Effects
Buchanan, 1986[97]	Rat	Day 9.5–9.75	1	Growth retardation, neural tube defects
Buchanan, 1989[50]	Rat	Day 10.6	1	None
Akazawa, 1989[49]	Rat embryo culture	Day 10.3	1	Growth retardation, neural tube defects
Smoak, 1990[98]	Mouse embryo culture	Day 8	2–29	Growth retardation, neural tube defects
Taganawa, 1991[51]	Rat	Day 9.5–10.5	2	Skeletal malformations
Peet, 1996[53]	Mouse embryo culture	Day 10–12	6	Increased cardiac lactate
Smoak, 1997[52]	Mouse embryo culture	Day 8.5–10.5	6	Cardiac malformations
Edwards, 2001[55]	Sheep	Late gestation	2	Increased ACTH

that during embryogenesis, the heart is dependent on glucose for energy production. Initially, energy production is primarily dependent on glycolysis prior to switching to the Krebs cycle and oxidative phosphorilation.[53] Exposure to hypoglycemia during this early glycolysis-dependent phase is associated with increased levels of lactate in the heart, which may be the proximate cause of the observed hypoglycemia-associated cardiac defects.

Besides the possible teratogenic effects of hypoglycemia on embryogenesis, maternal hypoglycemia may affect the fetus in several other ways. Gardner et al.[54] have demonstrated that in the ovine fetus, exposure to sustained hypoglycemia alters the capacity of the fetus to respond to repetitive episodes of acute hypoxemia. Edwards et al.[55] studied the responses of the fetal pituitary–adrenal axis to acute and chronic hypoglycemia in sheep. They found that the threshold for activation of the fetal ACTH response to acute hypoglycemia changes with increasing gestational age: as gestational age progresses, the fetus acquires an increased capacity to sense low glucose concentrations and activate the pituitary–adrenal response. Indeed, fetal sheep with low plasma glucose concentrations have higher plasma cortisol concentrations. This exposure of the fetus to excess glucocorticoid concentrations may program permanent changes in the fetal cardiovascular, endocrine, and metabolic systems that could result in a higher risk of adult pathophysiology.[56]

Despite the aforementioned potentially adverse effects of hypoglycemia on the fetus, the fetus may have the ability to protect its developing brain from acute hypoglycemia. Das et al.[57] have shown that the level of the insulin-insensitive glucose transporter Glut-1 in the brain increases in response to hypoglycemia. Furthermore, Lapidot et al.[58] found that when pregnant rabbits were made acutely hypoglycemic, the fetuses were able to maintain energy metabolism by utilizing lactate as a substrate.

In summary, studies in animal models have demonstrated that hypoglycemia may affect the developing fetus in a time and duration dependent fashion, both at the structural and the functional level. Whether these observations have any relevance to human pregnancy is, as yet, undetermined.

THE EFFECTS OF MATERNAL HYPOGLYCEMIA ON THE FETUS: HUMAN PREGNANCY

Although concerns regarding the hazards of hypoglycemia are primarily related to the pregnant diabetic patient herself, the potential effects of maternal hypoglycemia on the developing fetus need to be considered. As glucose freely traverses the placenta by facilitated diffusion, fetal glucose concentrations closely mirror maternal concentrations, and maternal hypoglycemia is necessarily associated with fetal hypoglycemia. In light of the data presented above suggesting a teratogenic effect of hypoglycemia in animal models, and considering the high incidence of maternal hypoglycemia during the first half of pregnancy, the possibility of an adverse effect of hypoglycemia on the developing human embryo becomes a matter of concern. However, the impact of maternal hypoglycemia on human fetal development and neonatal outcome has not been extensively studied. An early report on women undergoing psychiatric treatment with insulin shock therapy suggested an association between severe hypoglycemia induced during the first trimester and adverse pregnancy outcome.[59] However, since that report, not one of the studies involving pregnant women with type 1 diabetes has found any association between maternal hypoglycemia and adverse fetal outcome.[33,34,39,60,61] In our own study involving 84 women with type 1 diabetes, we specifically analyzed the possibility that severe maternal hypoglycemia in the first trimester might be associated with an increased risk of spontaneous abortion and major congenital malformations.[39] In this study, all 84 women were recruited prior to 11 weeks gestation, and 53 of them before seven weeks. We summarized the rates of spontaneous abortion and major malformations among subjects who did or did not have severe symptomatic hypoglycemia by 7, 9, 11, and 13 weeks' gestation. There were no congenital malformations among the offspring of women who had severe hypoglycemia in the first trimester. Furthermore, the rate of spontaneous abortion in this group was actually lower than among the women who did not have severe hypoglycemia, although this difference did not attain statistical significance (Table 33-2).

The aforementioned findings further support the observation that transient maternal hypoglycemia in human pregnancy, although very common, is not associated with embryonic demise or teratogenesis. Indeed, the effects of hypoglycemia on human pregnancy are most likely very different from the effects observed in rodents. Development in the rodent is primarily dependent on glycolysis during the period of neurulation but an analogous glycolytic dependence has not been clearly established in human embryos.[62] Furthermore, even among rodents there are variations in the responses of different species and different strains to altered

TABLE 33-2 First Trimester Severe Symptomatic Hypoglycemia, Spontaneous Abortions (SAB) and Congenital Malformations (CM)

Weeks	*N*	Patients With Severe Hypoglycemia	SAB	CM	Patients Without Severe Hypoglycemia	SAB	CM
7–8	53	2 (4%)	0/2 (0%)	0/2	51 (96%)	12/51 (24%)	1/39 (3%)
9–10	70	8 (11%)	0/8 (0%)	0/8	62 (89%)	17/62 (27%)	2/45 (4%)
11–12	84	11 (13%)	1/11 (9%)	0/10	73 (87%)	18/73 (25%)	2/55 (3%)
13	84	16 (19%)	1/16 (6%)	0/15	68 (81%)	18/68 (26%)	2/50 (4%)

Source: Adapted from Rosenn et al.[31]

glucose concentrations.[63] Thus, one needs to exercise great caution when attempting to apply findings from animal studies to human pregnancy.

Some controversy exists regarding the effect of maternal hypoglycemia on fetal biophysical characteristics in the third trimester of pregnancy. During a case of maternal hypoglycemic coma, Confino et al.[64] observed a pseudosinusoidal oscillating pattern with frequent decelerations followed by nonreactive tachycardia. Conversely, Matias et al.[65] observed a reassuring fetal heart rate (FHR) pattern with prolonged accelerations of great amplitude in their case report of a woman monitored during hypoglycemic coma at 29 weeks gestation. They suggested that this pattern may result from increased sympatheto-adrenergic activity in response to hypoglycemia, either maternal or fetal in origin.

In two separate reports, hypoglycemia in women with type 1 diabetes was associated with changes in fetal baseline heart rate[66] and heart rate variability.[67] Conversely, Reece et al.[68] performed insulin-induced hypoglycemic clamp studies in pregnant women with type 1 diabetes, lowering the blood glucose concentration to 45 mg/dL. During hypoglycemia, there was a nonsignificant increase in fetal limb and body movements, and no changes in fetal breathing movements or FHR. Other authors reported that insulin-induced maternal hypoglycemia was associated with increased frequency and amplitude of FHR accelerations[69] and fetal activity,[70] and with very slight or inconsistent changes in umbilical artery Doppler indices.[68,69]

Many clinicians believe that low maternal blood glucose levels are associated with a nonreactive FHR tracing and that maternal oral intake may improve the chances of it becoming reactive. In fact, there is conflicting evidence regarding this matter. Zimmer et al.[71] found that ingestion of 50 g oral glucose in 27 healthy pregnant women at 37–40 weeks gestation was followed by a decrease in FHR indices of variation. Similarly, Holden et al.[70] found that maternal hyperglycemia did not stimulate FHR accelerations. Other authors found increased reactivity,[72,73] increased mean FHR[74] or no difference[75] after ingestion of glucose.

In summary, there is considerable controversy in the literature regarding the effects of maternal hypoglycemia on fetal behavior and outcome. It is, however, reassuring that transient maternal hypoglycemia does not appear to affect embryonic survival and embryogenesis, even when it is severe and symptomatic.

MANAGEMENT OF HYPOGLYCEMIA

General Considerations

It is incumbent on health providers caring for pregnant women with diabetes, particularly those with type 1 diabetes, to be thoroughly knowledgeable about the characteristics and the management of hypoglycemia and to save no effort in educating patients and their families on these matters. At the time of the initial visit, that ideally should take place prior to pregnancy, the patient should be questioned about her history of hypoglycemic episodes, what kind of symptoms she usually experiences, whether she has primarily adrenergic symptoms or whether she has neuroglycopenia and requires assistance from other people, at what level of blood glucose do hypoglycemic symptoms usually occur, and how she usually treats hypoglycemia. This will provide basic information that may indicate how likely she is to experience severe hypoglycemia during pregnancy. A history of severe hypoglycemia in the year preceding pregnancy and self-reported hypoglycemia unawareness are strongly associated with severe hypoglycemia in pregnancy.[43] But even in women who have not had recent experience with severe hypoglycemia, it is important to emphasize to the patient and her family that the characteristics of hypoglycemia may change during pregnancy: institution of strict glycemic control increases the risk of hypoglycemia, the responses to hypoglycemia are diminished, and the phenomenon of hypoglycemia unawareness increases. All these require thorough understanding by the patient and her family of the measures that need to be taken to prevent and treat hypoglycemia. The patient's immediate family and coworkers should learn to recognize symptoms of hypoglycemia and how to respond when hypoglycemia occurs. The dangers of nocturnal hypoglycemia should be emphasized, and the patient should be encouraged to avoid sleeping alone. If the patient routinely spends the day at home on her own, family or friends should establish a routine of checking on her several times during the day. All patients should have a glucagon emergency kit (see below) available at home and at work, and the family and coworkers should be familiar with its use.

Prevention of Hypoglycemia

Frequent determinations of glucose concentrations are essential if one is to maintain strict glycemic control while avoiding hypoglycemia. Although many patients with type 1 diabetes may be used to checking glucose levels 3–4 times a day, it is practically impossible to maintain the level of strict control required in pregnancy without committing to self-monitoring at least 6–7 times a day. Because patients with type 1 diabetes are usually quite sensitive to insulin, minor alterations in caloric intake, insulin dose, or physical activity may induce surprisingly large alterations in blood glucose concentrations. This is particularly true during the first half of pregnancy, before the characteristic insulin resistance of pregnancy begins to develop. Thus, many patients with type 1 diabetes experience varying glycemic responses on different occasions to apparently identical quantities of carbohydrate intake. A specific dose of insulin that proved adequate for a specific meal on one occasion, may be too small or too large for the very same meal on another occasion, and result in either hyperglycemia or hypoglycemia. Understandably, patients tend to overcorrect with insulin when they encounter high levels of blood glucose resulting in inadvertent hypoglycemia, or to ingest excessive amounts of glucose in trying to overcome the unpleasant symptoms of hypoglycemia. Thus, the patient sets in motion cycles of alternating hyperglycemia and hypoglycemia resulting in wide glucose "excursions." By increasing the frequency of glucose testing, the patient can fine tune the boluses of insulin required to maintain strict control while responding to downward and upward trends of blood glucose in a timely and measured fashion. Indeed, some patients self-monitor glucose levels 10–12 times a day and inject small boluses of rapid acting insulin (either by syringe or insulin pen or through a continuous subcutaneous insulin pump) several times a day. The newer ultra-rapid insulin analogs (e.g., aspart or lispro) appear to be particularly suited for this kind of rapid-response strategy. If a dose of intermediate-acting insulin (neutral protamine Hagedorn [NPH]) is taken in the evening, it should be taken close to bedtime rather than at dinnertime to help avoid nocturnal hypoglycemia. Patients

who have difficulty in controlling the morning fasting glucose level should check glucose level at 3–4 o'clock in the morning. This will help to determine the causes of glucose instability and help guide the appropriate management.

In nonpregnant individuals with well-controlled type 1 diabetes, use of continuous subcutaneous glucose monitoring is associated with significantly less time spent in the hypoglycemic range (60 mg/dL or less).[76] However, such a benefit was not demonstrated in a randomized trial that included 123 pregnant women with type 1 diabetes and 31 with type 2 diabetes who were randomized to self-monitoring or intermittent monitoring with a continuous glucose monitor. The incidence of severe hypoglycemia was 16% in both these groups.[77] Despite these data, using a continuous glucose sensor can often help the patient detect downward or upward glucose trends, and an alarm may alert her to impending hypoglycemia. Analysis of the continuous glucose monitor can also aid the care provider in fine-tuning the insulin doses by providing comprehensive and continuous glucose data.

Treatment of nonpregnant individuals with type 1 diabetes with rapid and long-acting insulin analogs has been associated with a decrease in the incidence of severe hypoglycemia. Data on the use of insulin analogs in pregnancy are available from prospective and retrospective studies. A small retrospective study described the use of insulin lispro in 62 pregnant women with type 1 diabetes and reported that 14 (23%) had at least one episode of severe hypoglycemia.[78] A multicenter, multinational trial reported on 322 pregnant women with type 1 diabetes who were recruited either prior to pregnancy or during the first 10 weeks of pregnancy.[79,80] All enrollees were treated with NPH insulin once or twice daily and were randomized to additional treatment with multiple doses of either regular human insulin or insulin aspart. Major (severe) hypoglycemia occurred among 24.2% of those randomized to aspart compared to 21.2% of those randomized to regular insulin (nonsignificant difference). The rate of severe hypoglycemia was 1.4 per patient-year in the aspart group compared to 2.1 in the regular insulin group, again a nonsignificant difference. The authors estimated that treatment with aspart was associated with a 28% reduction in overall number of severe hypoglycemic episodes, and a 52% reduction in nocturnal episodes, both of which did not attain statistical significance. A subsequent analysis of the results of this trial sought to determine the effect of preconceptional randomization compared to randomization in early pregnancy.[81] Patients randomized preconceptionally to aspart had lower rates of severe hypoglycemia (0.9 per patient-year) in the first half of pregnancy compared to those randomized to regular insulin (2.4 per patient-year), as well as during the second half of pregnancy (0.3 vs. 1.2, respectively). However, these differences did not attain statistical significance. Another smaller study in which women were assigned preconceptionally to treatment with insulin lispro or regular human insulin found no difference in the rates of maternal hypoglycemia reported by patients.[82] In 24-hour glucose profiles performed during the first trimester, more women in the lispro group (56%) had no episodes of hypoglycemia compared to the human insulin group (38%), but this difference was not statistically significant. It seems that more data are necessary to determine conclusively whether use of rapid acting insulin analogs in pregnancy may decrease the incidence of hypoglycemia.

Glargine and detemir are two long-acting insulin analogs that have been used and studied in pregnant women. In a recent prospective observational study from Brazil,[83] a group of 56 women with pregestational diabetes and 82 with gestational diabetes were treated during pregnancy with either glargine or NPH combined with a rapid acting insulin analog. In the pregestational group, severe hypoglycemia occurred in 10 of the 38 (27%) women treated with NPH, but in none of the 18 treated with glargine. Severe hypoglycemia occurred in one woman with gestational diabetes treated with NPH. In a recent multicenter multinational prospective study, 310 pregnant women with type 1 diabetes were randomly assigned either preconceptionally or in early pregnancy to treatment with either NPH or detemir in combination with aspart before meals.[84] Although fasting glucose at 24 weeks gestation was lower in the group treated with detemir, there was no difference in the incidence of severe hypoglycemia (16% of women in the detemir group and 21% in the NPH group). There was also no difference in the rate of nocturnal hypoglycemia.

Continuous subcutaneous insulin infusion (CSII) with an insulin pump in individuals with type 1 diabetes is associated with a reduced rate of severe hypoglycemia without adversely affecting the level of glycemic control.[85] It is less certain whether treatment with an insulin pump during pregnancy can attain the same effect. Coustan et al.[86] randomized 22 pregnant women to either multiple dose injections or CSII and found no differences with respect to glycemic control, fetal outcome, or the frequency of adverse events, including maternal hypoglycemia. Similar results were reported by Carta et al.[87] Gabbe et al.[89] found that maternal and perinatal outcomes in women who started using CSII during pregnancy was comparable to outcomes in women who started CSII therapy prior to pregnancy or women on multiple-dose insulin therapy. Switching to CSII during pregnancy appeared to decrease the incidence of severe hypoglycemia. In a recent retrospective case-control study from Poland,[90] 64 pregnant women with type 1 diabetes treated with an insulin pump were matched with 64 women treated with multiple daily insulin injections. The incidence of hypoglycemia (less than 60 mg/dL) was similar in both groups in each of the 3 trimesters, but the incidence decreased significantly in the insulin pump group during the course of pregnancy. Lapolla et al.[91] compared 25 women who were treated with CSII to 68 women who were treated with conventional intensive insulin therapy during pregnancy. They found no significant differences between the two groups in metabolic control and maternal outcome. However, in this nonrandomized study, it appeared that women on CSII tended, a priori, to have more brittle diabetes and more advanced disease. The authors concluded that this mode of therapy allows better metabolic control in complicated cases where conventional multidose insulin therapy proves more problematic. These observations are in line with the empiric experience of most seasoned clinicians: CSII is not a panacea for brittle patients who are difficult to control and does not resolve the problem of hypoglycemia. It does not obviate the need for frequent determinations of glucose concentrations, and it certainly requires that the patient fully comprehend the dynamics of her disease and the mechanics of the pump. Nevertheless, there are some patients who seem to benefit greatly from CSII therapy and learn to use it efficiently while stabilizing their glycemic control and decreasing the incidence of severe hypoglycemia.

The desire to develop an "artificial pancreas" that will mimic the response of the human pancreas and regulate the delivery of

insulin based on the blood glucose concentration has led to the development of closed-loop systems. In these systems, computerized algorithms link insulin delivery by a pump to the input obtained from a continuous glucose monitor, or suspend insulin delivery when glucose sensor values reach a predetermined threshold. Studies in children and adults have demonstrated the potential of these systems to decrease the incidence of nocturnal hypoglycemia.[92,93] Two small studies in pregnant women with type 1 diabetes have demonstrated that closed-loop systems are effective in maintaining good glycemic control while avoiding nocturnal hypoglycemia.[94]

During labor, insulin requirements may change rapidly both due to the energy expended by the laboring woman and because most patients are kept fasting during active labor. On admission to the labor and delivery unit, women with type 1 diabetes should be placed on an insulin drip protocol. A suggested protocol is depicted in Figure 33-3. Capillary glucose concentrations should be monitored frequently (at least every hour, or more frequently if glucose levels are rising or declining) and the insulin drip should be adjusted accordingly with addition of 5% dextrose, as needed, to avoid hypoglycemia. Following delivery, insulin doses are best returned to slightly less than the prepregnancy doses with frequent monitoring of glucose levels.

Treatment of Hypoglycemia

Oral carbohydrate intake is the most common method of overcoming hypoglycemia, and in the vast majority of cases, it is the only one needed. Approximately 10–15 g of a simple carbohydrate in the form of simple sugar cubes, glucose tablets, orange juice, or a similar substance are usually sufficient to raise the level

1. Add 75 units regular human insulin to 500 ml normal saline obtaining a concentration of 0.15 units/cc.
2. Discard 100 cc of this solution through the IV tubing.
3. Place this solution on an infusion pump and start IV.
4. Run supplementary solution (D5LR) through another infusion pump and piggyback the insulin line into this line **as close to the arm as possible** and run at 30 cc/hr.
5. Do not run any additional fluids through this line.
6. Obtain patient's fingerstick blood sugar every hour and adjust insulin infusion rate accordingly, based on the following scale: (The goal is to maintain patient's blood glucose 70-100 mg/dL):

Glucose mg/dL	Infusion Rate ml/hr	Insulin units/hr
75 or less	0	0
76-85	4	0.6
86-100	8	1.2
101-120	12	1.8
121-140	16	2.4
141-160	20	3.0
161-200	30	4.5
201-240	40	6.0

7. If patient's blood glucose is lower than 75 mg/dL, insulin should be off, and D5LR should be adjusted:

Glucose mg/dL	D5LR Infusion Rate (ml/hr)
71-75	30
66-70	60
61-65	90
56-60	120
51-55	150
46-50	180

8. Increase frequency of fingerstick to every 30 minutes, and inform MD if:
   Blood glucose > 200 mg/dL or < 75 mg/dL
   Blood glucose is rising or failing rapidly
   Total fluid intake exceeds 125 cc/hr

Figure 33-3 Protocol for IV insulin infusion in labor.

of glucose in the blood and abort the hypoglycemic event. Most often, the patient herself will become aware of the evolving hypoglycemic event and will be prompted by the adrenergic symptoms to ingest a carbohydrate-rich substance. However, in patients who suffer from hypoglycemia unawareness, it is often the people around who first notice the manifestations of neuroglycopenia: the patient starts acting in a somewhat bizarre manner, may demonstrate inability to concentrate or respond in a clear manner, or may actually have slurred speech. Family members and close associates often learn to recognize the signs of hypoglycemia and will encourage the patient to eat something. The hypoglycemic patient will often resist these attempts and deny being hypoglycemic, but an immediate determination of the glucose concentration will quickly settle the matter. It is important for the patient to continue and eat some food (a combination of carbohydrate with protein or fat) to maintain an acceptable level of blood glucose and to recheck the glucose level within a short period of time to determine the trend of blood glucose and respond accordingly. The urge to overcorrect the hypoglycemia with excessive carbohydrate intake should be avoided, as it tends to initiate a cycle of excessive glucose excursions.

Sometimes the degree of hypoglycemia is such that the patient is unable to correct it herself; she may either be obtunded to a degree that does not enable her to drink or eat or she may actually be unconscious. Under these circumstances, the best approach is to inject glucagon available as a glucagon emergency kit. These kits are readily obtainable by prescription at pharmacies and are stable for at least two years when stored at room temperature. The kit contains 1 mg of glucagon in lyophilized form that is dissolved in 1cc of solution in a presterilized syringe that is part of the kit. The glucagon may be injected subcutaneously, intramuscularly, or intravenously and will raise the blood glucose concentration within minutes by acting directly on the liver to promote glycogenolysis. A patient in hypoglycemic coma will usually regain consciousness within 10 minutes of receiving glucagon and should then be fed carbohydrate to prevent a relapse.

Although glucagon is an excellent mode of treatment for the unconscious or semiconscious patient in a setting that does not enable intravenous access, its efficacy in situations of prolonged hypoglycemic coma is less certain.[95,96] In these circumstances, intravenous administration of approximately 50 mL of 50% dextrose provides 25 g of dextrose and will cause almost all patients to regain consciousness in a matter of minutes. The only patients

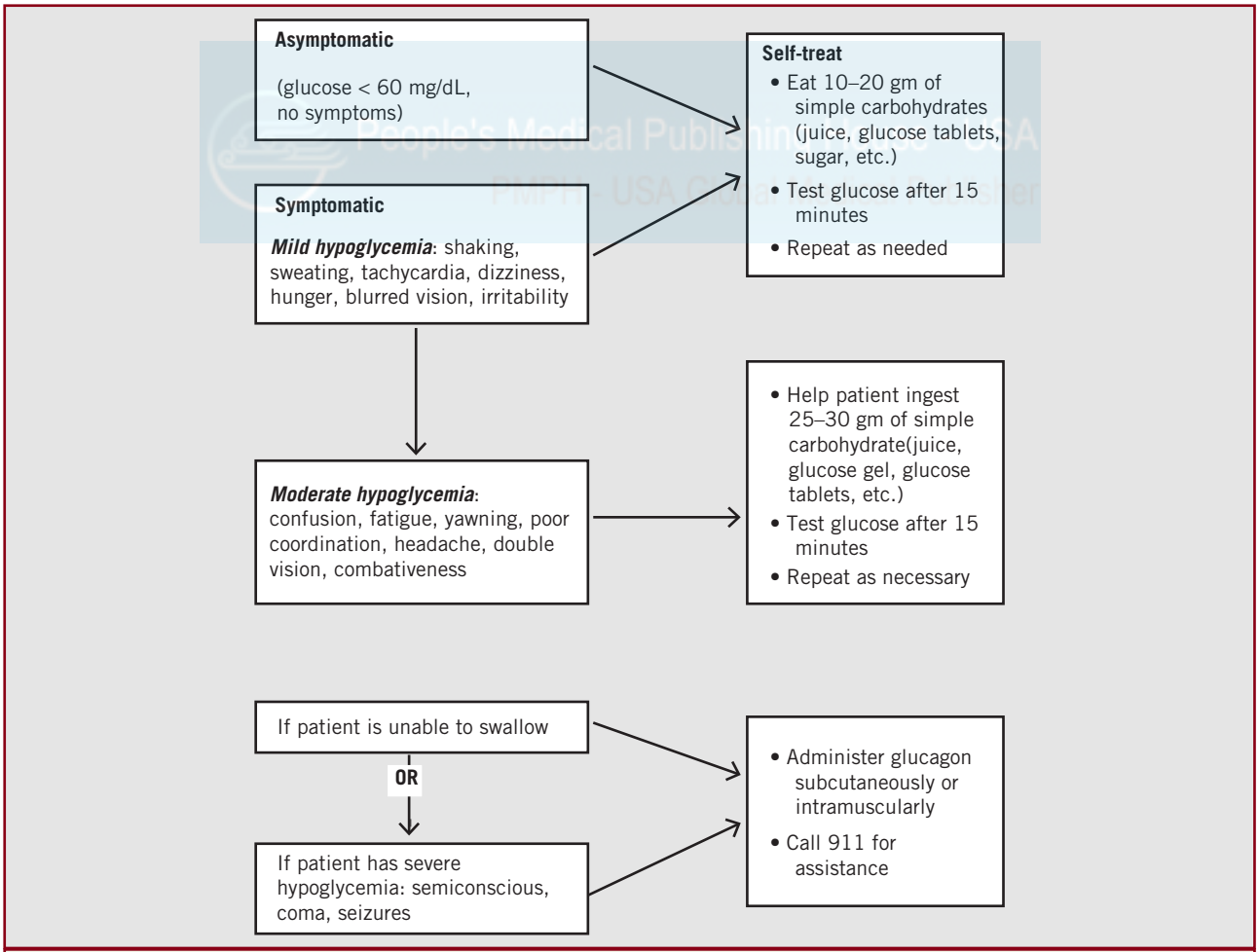

Figure 33-4 Treatment of hypoglycemia.

who do not respond to intravenous dextrose are those who have cerebral edema, a rare and severe complication of prolonged hypoglycemic coma that carries a poor prognosis. A suggested treatment algorithm for hypoglycemia is presented in Figure 33-4.

SUMMARY

Several clinical studies have demonstrated the beneficial effects of improved glycemic control on pregnancy outcome in women with diabetes. Intensive insulin therapy in these pregnancies is now widely advocated, and commonly accepted as the best approach most likely to optimize pregnancy outcome. At the same time, it is important to recognize the potential risks of this approach in women with diabetes who are prone to severe hypoglycemia. It is presently unknown what level of glycemia conveys the benefits of improved glycemic control in terms of pregnancy outcome without increasing the risk of hypoglycemia. It would, therefore, be prudent to exercise a measure of caution in setting goals of glycemic control for the occasional patient who demonstrates a tendency to have recurrent episodes of severe hypoglycemia that cannot be resolved with the usual tactics of modifying insulin regimens, caloric intake, and physical activity.

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34

Diabetic Retinopathy

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Of all the senses, sight must be the most delightful.

—Helen Keller

Key Points

- Diabetic retinopathy (DR) may progress during pregnancy and serial retinal examinations are essential
- Adequate glycemic control at conception significantly decreases the risk of retinopathy progression
- Retinal status at conception predicts the likelihood of retinopathy progression
- Longer duration of diabetes increases the risk for retinopathy progression
- Large improvement in glycemic control early in pregnancy may increase the risk of retinopathy
- Maternal and fetal outcomes can be optimized with adequate preconceptional glycemic control, blood pressure (BP) control, and evaluation of retinal disease
- Pregnancy has no long-term effects on the development or progression of DR

INTRODUCTION

Diabetic retinopathy (DR) is the leading cause of incident blindness among adults in the United States.[1] Worldwide, there are approximately 93 million people with DR, including 28 million with advanced vision-threatening stages of the disease.[2] DR is due primarily to vascular effects of chronic hyperglycemia, leading to retinal injury and ischemia. Therapy can both limit disease progression and improve visual defects. However, the majority of DR patients are asymptomatic until late stages of the disease, underlining the role of early screening and intervention to limit vision loss. The interaction between pregnancy and DR has long been a matter of controversy. Although there is evidence for progression of DR during pregnancy, most changes are transient and reversible. This chapter will review the natural history of DR and focus on its interplay with pregnancy, highlighting both short- and long-term outcomes.

PATHOGENESIS

Pathogenesis of DR is multifactorial, but ultimately due to the metabolic effects of chronic hyperglycemia.[3] The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) found that intensive insulin therapy reduced the incidence of DR in subjects with type 1 and type 2 diabetes mellitus, respectively. In both studies, these improved outcomes were directly related to glycemic control, as assessed by glycosylated hemoglobin (HbA1c).[4–6]

DR is broadly classified as either proliferative or nonproliferative, based on the presence or absence of retinal neovascularization. Further stratification of disease severity, used more in research than in clinical practice, is based on objective retinal findings as outlined in Table 34-1.[7] Early retinal lesions are often reversible, becoming fixed with more advanced and chronic DR. Nonproliferative abnormalities range from increased permeability and local edema to moderate and severe nonproliferative diabetic retinopathy (NPDR), characterized by vessel closure and ischemia. Loss of vision in NPDR is due primarily to macular edema. Proliferative diabetic retinopathy (PDR), with neovascularization of the retina and the posterior surface of the vitreous body, may progress to preretinal and vitreous hemorrhage, subsequent fibrosis, and possible retinal detachment. PDR may occur *de novo* or in the setting of prior or coexisting nonproliferative changes. Transient vision loss in PDR may result from acute hemorrhage; in most cases, vision will clear following reabsorption. More permanent visual loss is usually related to retinal detachment or to macular ischemia.

Within the retina, hyperglycemia mainly affects the microvascular endothelial cells (ECs).[8,9] Animal models suggest that initial exposure of ECs to chronic hyperglycemia leads to the loss of capillary pericytes.[10] This leads to the formation of microaneurysms and vascular closure due to the increased thrombogenicity of the endothelial surface.[11,12] The ensuing retinal ischemia promotes angiogenesis and neovascularization. Several mechanisms may mediate these changes. Nonenzymatic glycosylation of serum or tissue proteins in the setting of hyperglycemia leads to irreversible formation of advanced glycosylation end products (AGEs),[13]

TABLE 34-1 Classification of DR

Disease Severity Level	Findings on Dilated Ophthalmoscopy
No retinopathy	No abnormalities
Mild NDPR	Microaneurysms only
Moderate NDPR	More than just microaneurysms but less severe than severe NPDR
Severe NDPR	Microaneurysms and any of the following:
	Extensive retinal hemorrhages in each quadrant
	Venous beading in two or more quadrants
	Prominent intravascular microvascular abnormalities in one or more quadrants
	And no signs of proliferative retinopathy
PDR	Neovascularization
	Vitreous/preretinal hemorrhage

which can initiate a signaling cascade leading to oxidative stress and microvascular inflammation. The interaction between AGEs and tissue collagen has been implicated in the initiation of microvascular complications.[14] Likewise, certain experimental and animal models of retinopathy have suggested a role for insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF), produced in response to tissue hypoxia, in mediating retinal neovascularization.[15,16] Increased retinal blood flow in advanced DR, likely due to a loss of the retinal autoregulation,[17] leads to increased shear stress which, in turn, promotes secretion of vasoactive factors and vascular leakage. In diabetes, vascular endothelium demonstrates an imbalance in hemostasis due to impaired synthesis of vasodilators, increased release of vasoconstrictors, and activation of the renin–angiotensin system.[18] In the retina, such changes facilitate ischemic injury and can lead to vascular leakage.[17] Additionally, genetic and ethnic factors influence an individual's susceptibility to retinopathy, with a higher prevalence in individuals with a family history of DR, and those of African–American or Hispanic descent.[6,19,20]

NATURAL HISTORY OF DR

The Wisconsin Epidemiologic Study of Diabetic Retinopathy first described the natural history of DR. Started in the 1980s, this effort included 99% of clinicians in an 11-county area of southern Wisconsin, who followed over 10,000 diabetic patients. It described the prevalence of diabetic complication in patients treated with then-conventional therapy.[21,22] In patients with type 1 diabetes, the onset of DR followed diagnosis of type 1 diabetes mellitus (DM) by three to five years, occurring in almost all patients by 15–20 years. By contrast, patients with type 2 diabetes appeared to have developed retinopathy four to seven years before the clinical diagnosis of diabetes, perhaps due to prolonged antecedent prediabetes, or to comorbid vascular risk factors, as occurs in diabetic nephropathy. DR prevalence increased progressively with increasing duration of either type 1 or type 2 DM.[21,22]

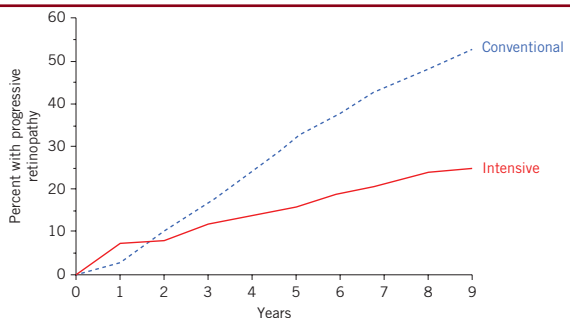

Figure 34.1 Retinopathy progression in the DCCT trial: intensive treatment with initial worsening of retinopathy, but overall slower progression. (From Ref.[4])

More recent studies (DCCT and UKPDS), comparing more intensive to then-conventional glycemic targets, found that glycemic control was a major determinant for the development and progression of DR in patients with type 1 and type 2 diabetes.[4,5] Follow-up cohorts from Wisconsin also revealed decreased prevalence of retinopathy 8–10 years after diagnosis with initiation of therapy and a lower rate of severe retinopathy with newer treatment strategies.[23,24] The DCCT also concluded that intensive insulin therapy was associated with worsening retinopathy in the first year following initiation of therapy (Figure 34-1).[4] However, there was no evidence that subjects with more rapid reduction of HbA1c had a greater risk of early worsening of retinopathy than those with more gradual reduction, when the reductions were of similar magnitude. In subjects with early worsening of DR, retinal examinations revealed an increased number of soft exudates.[25] Interestingly, this effect was short-lived, with improved retinopathy at two years when compared with subjects receiving conventional therapy. The mechanisms that may contribute to early retinopathy progression are uncertain. Rapid normalization of hyperglycemia appears to increase EC apoptosis.[26,27] In addition, narrowed vessels are thought to be more sensitive to a decreased plasma volume with correction of hyperglycemia, perhaps leading to small vessel collapse, superficial retinal infarcts and the soft exudates which are observed clinically.[25]

RISK FACTORS FOR RETINOPATHY DEVELOPMENT AND PROGRESSION

As noted previously, diabetes duration is closely associated with the presence and type of retinopathy. Background retinopathy is estimated to develop in 46% of type 1 diabetes patients within five years, and 75% within 10 years from the time of diagnosis. Proliferative retinopathy rarely develops in the first five years after diagnosis, but has been noted in 15% of patient by 15 years and in 55% by 20 years from the time of diagnosis.[21,22] Similarly, the age at the time of retinal examination is related to the severity of retinopathy.[28] Not surprisingly, the severity of retinopathy at the start of an observation period is predictive of subsequent progression.[29] Hyperglycemia and elevated levels of HbA1c are also associated with an increased risk of retinopathy.[4] Coexistent hypertension has also been linked to progression and severity of DR.[30,31] Antihypertensive regimens meant to slow the progression of nephropathy appear to also delay the progression of retinopathy.[32]

DR IN PREGNANCY

The pathogenesis of DR during pregnancy is multifactorial. Pregnancy is a state of hyperdynamic circulation due to vasodilation occurring early in gestation. A higher cardiac output, increased plasma volume and blood flow are also typical.[33] In the absence of diabetes, autoregulatory mechanisms are activated and retinal blood flow (RBF) is unchanged. However, in pregnancies complicated by diabetes, retinal autoregulation is lost[34] and RBF is increased.[35] Increased RBF is associated with a higher degree of DR severity during pregnancy.[36] Pregnancy is also characterized by a gradual increase in BP starting at 20 weeks of gestation and approximately 10%–20% of women with diabetes have preexisting or new onset hypertension during pregnancy. Hypertension during pregnancy and preeclampsia are both associated with a higher risk of retinopathy progression.[37,38] Changes in circulating hormones and growth factors during pregnancy may also have an effect on the progression of retinopathy. The placenta is a source of angiogenic factors that result in vessel proliferation. Human placental lactogen and insulin-like growth factors have growth hormone-like actions and may contribute to retinopathy progression.[39–41] When secreted in very high levels during pregnancy, they may theoretically stimulate new vessel formation in the retina. Endocrine effects of the feto-placental unit play a particular role in the development of insulin resistance during pregnancy.[42,43] Even in healthy women, insulin sensitivity decreases by 40%–50% during the third trimester.[44] In women with pregestational diabetes, insulin requirements increase steadily throughout gestation, especially for subjects with type 2 diabetes.[45,46] Faced with these metabolic changes, intensive glucose control is the cornerstone of diabetes management in pregnancy. Glycemic control is necessary to improve obstetric, fetal, and neonatal outcomes. Similar to nonpregnant populations, rapid institution of intensive glucose control may accelerate retinopathy progression transiently.[25]

Despite the hormonal, physiological, and metabolic changes that occur, careful review of the evidence is necessary before concluding that pregnancy per se acceleratess DR progression. Most of the research on DR in pregnancy was completed in cohort studies. Differing study design, control groups used for comparison, fundoscopic examination method, and, most importantly, length of follow-up following delivery may explain the large variability in conclusions on the effect of pregnancy on DR. Reported rates of retinopathy progression range between 5% and 70%.[47–54] Although we acknowledge the limitations of this body of research, some findings emerged to shed light on the risk factors for progression of DR in pregnancy.

RISK FACTORS FOR DEVELOPMENT AND PROGRESSION OF RETINOPATHY DURING PREGNANCY

Severity of Preexisting Retinal Disease

DR progression was related to the severity of preexisting retinopathy before conception in the Diabetes in Early Pregnancy Study.[55] Ten percent of women without DR at baseline progressed to NPDR, but none progressed to PDR. In women with baseline minimal DR (i.e., microaneurysms), 20% experienced worsening of NPDR and 3% developed PDR. By contrast, 50% of women with moderate NPDR at baseline progressed to more severe NPDR during pregnancy and 25% developed PDR. A summary of other studies supporting the association between DR progression in pregnancy and severity of retinopathy is presented in Table 34-2. Due to their observational design and the lack of control groups, these studies do not enable us to ascertain whether progression would have occurred without pregnancy. In a prospective controlled study, Klein et al. found no difference in DR prevalence comparing early pregnant women (43%) and nonpregnant controls (39%), despite better glycemic and BP control in the pregnant women.[50] However, their results were not stratified by initial retinal disease. Regression analysis controlling for baseline HbA1c, but not for baseline DR, suggested a twofold increased risk of DR progression in the pregnant group, with a follow-up at approximately nine weeks postpartum.

Since several studies have described regression of retinal changes in the postpartum period,[37,48,53,56] duration of follow-up postpartum may significantly impact our interpretation of studies aimed at assessment of DR progression due to pregnancy. In women with mild DR, the rates of both microaneurysm formation and disappearance increase during pregnancy. The microaneurysm count is greatest at three months postpartum, but the rate of disappearance exceeds that of formation six months postpartum,[57] suggesting that effects of pregnancy on DR may be short-lived.

Duration of Diabetes

Not surprisingly, risk factors for DR progression in nonpregnant individuals also apply in the setting of pregnancy. The Diabetes in Early Pregnancy Study demonstrated a gradual increase in the risk of DR progression with longer duration of diabetes with a peak at 15–20 years.[55] Women with disease duration of 0–5 years, 6–10 years, 11–15 years, 16–20 years, and more than 20 years had risks of progression of 5%, 14%, 34%, 45%, and 36%, respectively. By comparison, PDR occurred in only 18% of women with diabetes for less than 15 years compared with 39% of women with diabetes for over 15 years. Conversely, women who experienced DR progression in pregnancy had longer duration of diabetes compared to women without progression.[53] A recent cohort study also found that DR progression was significantly greater in women with diabetes for 10–19 years compared to those with the disease for less than 10 years (10% vs. 0%, $P = 0.007$).[47] The study also included 20 pregnancies in women with diabetes for more than 20 years, who had no or mild retinopathy at the time of conception. Only one of these women experienced DR progression, highlighting the importance of retinal status at the time of conception in predicting DR progression during pregnancy.

Glycemic Control

Several studies have determined that poor glycemic control before pregnancy and rapid control early in pregnancy are associated with a higher risk of DR progression.[55,58] In the Diabetes in Early Pregnancy Study, elevated HbA1c early in pregnancy was associated with a higher risk for DR progression.[55] Women with an HbA1c level 6 standard deviations above the control group's mean had double the odds of worsening DR (CI 1.1–7.2; $P = 0.039$). The study also concluded that DR progression was associated with the largest improvement in HbA1c between baseline and 14 weeks. In other studies, pregnant women with

TABLE 34-2 Progression of DR in Pregnancy Stratified by Initial Retinal Status

		Number and % With Progression by Initial Status					
	Number of Pregnancies	No Retinopathy		Background Retinopathy		Proliferative Retinopathy	
Horvat[69] (1980)	160	13/118	11%	11/35	31%	1/7	14%
Moloney[48] (1982)	53	8/20	40%	15/30	50%	1/3	33%
Dibble[51] (1982)	55	0/23	0%	3/19	16%	7/13	54%
Price[49] (1984)	31	0/14	0%	0/10	0%	5/7	71%
Ohrt[56] (1984)	100	4/50	8%	15/48	31%	1/2	50%
Jovanovic[45] (1984)	21	0/0	0%	0/11	0%	4/10	40%
Phelps[58] (1986)	38	3/13	23%	13/20	65%	5/5	100%
Serup[70] (1986)	45	6/19	32%	11/21	52%	0/5	0%
Rosenn[37] (1992)	154	18/78	23%	28/68	41%	5/8	63%
Chew[55] (1995)	140	4/39	10%	31/101	31%	*a*	
Axer-Siegel[53] (1996)	65	10/38	26%	17/22	77%	2/5	40%
Lovestam-Adrian[38] (1997)[b]	65	10/39	26%	3/14	21%	5/12	42%
Lapolla[71] (1998)	16	0/9	0%	1/7	14%	0/0	0%
Temple[47] (2001)	152	6/136	4%	3/10	30%	0/6	0%
Vestgaard[72] (2010)	102	8/38	21%	16/55	29%	4/9	44%
Rasmussen[73] (2010)	160	13/145	9%	3/15	20%	0/0	0%
Total	1357	103/779	13%	170/486	35%	40/92	43%

[a]Women with proliferative retinopathy were excluded from the study.
[b]Includes women with severe nonproliferative retinopathy.

good preconceptional glycemic control have a lower risk of DR progression (5%–6.3%).[47,59] A nested analysis of the DCCT, which focused on the effect of pregnancy, also evaluated the effect of pregnancy in 94 women treated with intensive therapy compared to 86 women who were assigned conventional therapy.[54] Upon confirmation of pregnancy, subjects were all treated with an intensive regimen. The study demonstrated more frequent worsening of DR in women who had been on conventional therapy before pregnancy compared to those who had received preconceptional intensive therapy (19.6% vs. 7.2%). These findings parallel the paradoxical worsening of retinopathy in the intensive therapy group during the first of the DCCT and emphasize the importance of tight preconceptional glycemic control.

Hypertension During Pregnancy

In a cohort of 154 women, worsening of DR was more frequent in women with hypertension compared to normotensive subjects (55% vs. 25%). Both elevated systolic and diastolic BP have been independently linked to DR progression.[38,50] Women with chronic hypertension had a 61% risk of DR progression, and those with preeclampsia a 50% risk.[37,38] Considering the high incidence of hypertensive disorders in women with pregestational DM, increased emphasis should be placed on BP control to limit DR progression.

Long-term Outcomes

Several studies have focused on the long-term outcomes of pregnancy in women with pregestational diabetes. The EURODIAB PCS (Prospective Complications Study) followed 793 women for 7.3 years and compared the outcomes of 63 women who became pregnant to those who did not conceive.[60] The presence and severity of retinopathy at the time of follow-up was predicted by duration of diabetes and HbA1c level, but not by history of pregnancy. A large retrospective study compared 776 nulliparous women to 582 parous women with type 1 diabetes.[61] The prevalence of retinopathy was lower in women who had two or more pregnancies (35%), compared to those who had only one pregnancy (45%), and those who did not conceive (48%). Similarly, PDR rates were lower in parous women (8%) compared to nulliparous subjects (16%). These differences persisted in analyses adjusted for glycemic control, suggesting that pregnancy is not a risk factor for long-term DR and its progression. A nested case–control study performed within the Pittsburgh Epidemiology of Diabetes Complications study found no difference in the prevalence of proliferative retinopathy between 80 parous women and matched nulligravid controls (35% and 36%); by contrast, there was a trend toward increased incidence of proliferative retinopathy in the small subset of women who had a pregnancy within the two-year

interval between study visits, underscoring differences between short- and long-term effects of pregnancy.[62] Rosenn et al. followed 81 women with type 1 diabetes, who had no or mild retinopathy at the time of their first pregnancy for a mean of 5.5 (1–15) years.[63] They estimated a 20% risk of incident or progressive DR within three years of pregnancy, similar to the expected rate in a general population of patients with diabetes. Proportional hazards models demonstrated that total parity was protective against DR progression ($P = 0.04$). The DCCT also demonstrated similar retinopathy rates between women who became pregnant and those who did not conceive, at an average follow-up of 6.5 years.[60]

SPECIAL CONSIDERATIONS DURING PREGNANCY

Gestational Diabetes

Women with only gestational diabetes are not at risk of DR during pregnancy because of the recent onset of their hypoglycemia. One report suggested that 50% of women with gestational diabetes exhibited retinal vessel tortuosity.[64] Although this may be a marker for those women who will later develop overt diabetes, further research is needed to confirm this hypothesis. Since gestational diabetes mellitus (GDM) may be diagnosed in women who actually have previously unrecognized or new-onset type 2 DM, these women should be screened for DM postpartum, and then counseled to undergo retinal examination if DM is diagnosed.

Fetal Growth Effects

Progression of DR during pregnancy has been associated with an increased risk for fetal growth restriction. In a study by McElvy et al., birth weight was reduced by a mean of 268 g, and the overall birth weight distribution shifted to the left in women with progressive DR, perhaps reflecting generalized microvascular disease.[65]

Considerations for Mode of Delivery

Another concern related to pregnancy is whether the abrupt changes in maternal BP during delivery may cause acute retinal hemorrhages in women with advanced DR. Some advocate cesarean delivery in these cases, albeit with little evidence. By contrast, a secondary analysis of 192 women with type 1 diabetes and close follow-up during pregnancy revealed no difference in DR progression from early or late pregnancy to postpartum comparing women who underwent elective cesarean delivery with those who had cesarean delivery before the second stage of labor and those who experienced a second stage of labor.[66] Since retinal vascular changes are predominantly postarteriolar, they are unlikely to be affected by Valsalva maneuvers including expulsive efforts in the second stage of labor. Vaginal delivery, if not otherwise contraindicated, should be considered in women with stable retinal status throughout their pregnancies.

Treatment of Retinopathy During Pregnancy

With adequate metabolic control and treatment of preexisting retinopathy, progression to sight-threatening DR during pregnancy is unlikely. Although there are no randomized trials of pregnancy in women with retinopathy to assess the indications and efficacy of laser photocoagulation therapy, insights may be extrapolated from the nonpregnant population. Current guidelines for nonpregnant individuals recommend laser photocoagulation for significant neovascularization of the optic nerve head or any neovascularization in the presence of vitreous hemorrhage. Also, laser therapy should be considered in cases with retinal neovascularization, or with severe nonproliferative retinopathy. A proactive treatment approach is recommended during pregnancy due to the risk of rapid progression with advanced disease or with newly tightened glycemic control. Women with completely regressed PDR, either spontaneously or following laser therapy, are very unlikely to experience further proliferation during pregnancy.[48,67] A monitoring strategy that includes close surveillance and early intervention is paramount to reduce sight-threatening DR progression in pregnancy.

Recommendation for Periconceptional Care

The most recent standards of medical care in diabetes suggest the following for care of pregnant women with diabetes[68]:

- If possible, HbA1c level should be as close to normal as possible (<7%) before conception is attempted.
- Women with diabetes, who are contemplating pregnancy should be evaluated and, if indicated, treated for DR, nephropathy, neuropathy, and cardiovascular disease.
- Reproductive age women with type 1 diabetes should have an initial dilated and comprehensive eye examination within five years of disease onset.
- Reproductive age women with type 2 diabetes should have an initial dilated and comprehensive eye examination soon after the diagnosis is made.
- Women with diabetes, who are contemplating pregnancy or those who have become pregnant should undergo a comprehensive eye examination and be counseled on the risks of incident or progressive DR during pregnancy.
- During pregnancy, eye examination should initially occur during the first trimester with close follow-up during pregnancy and for one year postpartum.
- If the initial retinal examination is normal, a repeat exam should be performed at approximately 28 weeks of gestation.
- If mild or moderate nonproliferative retinopathy is evident in early pregnancy, an additional examination should be performed at 16–20 weeks of gestation.
- Women with either macular edema or severe nonproliferative retinopathy should be referred to possible laser photocoagulation. More frequent monitoring, possibly with monthly examinations, may be required.
- To reduce the risk or slow the progression of retinopathy, the treatment strategy should focus on optimizing glycemic as well as BP control.

CONCLUSION

Progression of DR may occur transiently during pregnancy and the immediate puerperium. While the mechanisms for DR progression are not fully understood, risk factors include poor early pregnancy glycemic control, rapid correction, baseline retinal

status, duration of diabetes, and hypertension. Preconceptional control of glucose levels and BP, and treatment of retinal disease, when needed, are paramount in reducing the risk of DR progression. In itself, pregnancy does not appear to alter the course of retinopathy in women with diabetes.

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Diabetic Nephropathy in Pregnancy

35

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Superficially, it might be said that the function of the kidney is to make urine; but in a more considered view one can say that the kidneys make the stuff of philosophy itself

—Homer Smith

Key Points

- Pregnancy outcomes, including preeclampsia, prematurity, and intrauterine growth restriction, are worse in women with diabetic nephropathy (DN) than in those with diabetes mellitus(DM) alone.
- Decreased renal function and poorly controlled hypertension before conception and early in pregnancy can predict increased risk of poor outcomes in women with diabetic nephropathy.
- Pregnancy, per se, does not precipitate diabetic nephropathy nor accelerate its course in women with near-normal renal function at baseline.
- Similar to nondiabetic renal disease, pregnancy may accelerate the loss of renal function in women with diabetic nephropathy when renal function is compromised (serum creatinine ≥1.4 mg/dL or creatinine clearance <75 mL/min) at baseline.
- The diagnosis of preeclampsia is problematic in women with diabetic nephropathy who may exhibit hypertension, proteinuria, and decreased renal function at baseline.
- Outcomes may be improved when blood pressure(BP) and proteinuria are optimized by use of **angiotensin-converting-enzyme** (ACE) inhibitors until pregnancy is confirmed and by tight BP control throughout pregnancy.

INTRODUCTION

Diabetic nephropathy (DN) is the most frequent cause of progressive proteinuric renal disease and end-stage renal disease (ESRD) in Europe and the Americas. Improved medical care now allows many women with DN due to childhood type 1 diabetes mellitus (DM) to contemplate pregnancy. Likewise, an epidemic of type 2 diabetes mostly associated with obesity and the so-called "metabolic syndrome" also contributes to DN during childbearing years. In most patients, DN is accompanied by hypertension and other manifestations of macro- and microvascular disease. Maternal and fetal risks are increased in pregnancies complicated by diabetes alone, hypertension, vascular disease, or renal disease of any cause or severity[1,2]; these risks may be magnified in women with DN. Furthermore, although it is now clear that pregnancy seldom accelerates the loss of renal function in women with underlying nondiabetic renal disease in those cases where preconception renal function is well preserved and hypertension absent or well controlled,[3] it has been uncertain how we should best counsel women with DN regarding the effects of pregnancy on the progression of their renal disease.

In this chapter, we will first review briefly the natural history, classification, and pathophysiology of DN, focusing on the effects of medical intervention in nonpregnant patients and on how the renal physiologic changes which characterize normal gestation may interact with the diabetic kidney. Next, we will examine the available evidence regarding possible effects of pregnancy on the progression of DN, comparing it with studies of pregnancy in nondiabetic renal disease. We will then focus on pregnancy risks in women with DN. We will conclude with suggestions for key research questions whose answers may impact on the optimal care of these women.

NATURAL HISTORY AND PATHOPHYSIOLOGY

DN affects 30%–40% of patients with DM. Its natural history has been described best in patients with type 1 diabetes, and divided by Mogenson into five stages, based on clinical pathological and physiological characteristics.[4] Subsequently, the National Kidney Foundation developed consensus guidelines to promote recognition and clinical intervention in patients with chronic kidney disease (CKD) of any cause; these guidelines recognize five stages of CKD, based on the presence of renal damage and progressive decrements in glomerular filtration rate (GFR), in some cases subdividing them further.[5] Although others have suggested modifications to these classification schemes, which will be discussed below, Table 35-1 lists the stages of progressive DN and CKD in

these two predominant systems, with key clinical or pathologic findings.

Soon after the diagnosis of diabetes, renal and glomerular hypertrophy are the norm and renal hemodynamics are marked by hyperfiltration (increased GFR) with an increased filtration fraction (FF), that is, the increment in GFR exceeds that in renal plasma flow (RPF).[6] The elevated FF suggests that hyperfiltration is due in large part to increased efferent arteriolar resistance with resulting elevated intraglomerular capillary pressure; this "glomerular hypertension" has been shown to result in progressive scarring and nephron loss in several animal models of hypertension and progressive renal failure.[7] The progression of histopathologic changes over the first years of diabetes and hyperfiltration include thickening of the glomerular basement membrane, increased capillary wall area, then mesangial expansion.[8] Exercise-induced proteinuria is increased at the earliest stage of nephropathy, initially without evidence of albuminuria at rest. Clinical manifestations of disease appear reversible at this stage, as tight glycemic control can normalize both hyperfiltration and exercise-induced proteinuria.[9] The onset of persisting microalbuminuria (see below), readily detected in usual clinical practice, heralds "incipient nephropathy." Although microalbuminuria is commonly thought a marker of early renal disease, it actually occurs several years into the course of established and progressive diabetic nephropathy. Most patients with microalbuminuria due to type I diabetes appear to be normotensive; however, carefully controlled studies using 24-h blood pressure (BP) monitoring show their BP to be elevated significantly, albeit still within the "normal" range,[10] predicting more significant hypertension later, as renal disease progresses. Without special treatment, microalbuminuria often progresses to macroalbuminuria (≥300 mg/d) and "fixed" proteinuria (≥500 mg/d), though some studies suggest that tight control of multiple diabetic risk factors, including glycemia may lead to regression, even at this stage of disease.[11,12] DN may result not only in significant proteinuria, but is the most common cause of nephrotic-range proteinuria in adults. Clinically overt diabetic nephropathy is then characterized by hypertension and progressive decrements in GFR, leading to ESRD and markedly increased risk of cardiovascular morbidity and mortality.

The clinical evolution of nephropathy in patients with type 2 diabetes differs in that they are more likely to exhibit hypertension, microalbuminuria, and hyperlipidemia at baseline, or sooner after diagnosis; this may relate in part to the consequences of a prolonged period of insulin resistance before the diagnosis of frank diabetes or to the interacting effects of diabetes and hypertension in obese patients.[13] Many other patients with type 2 diabetes may suffer significant decrements in renal function, perhaps due to hypertensive nephrosclerosis rather than to DN and escape clinical recognition if physicians only screen for renal disease in patients with evidence of retinopathy or microalbuminuria.[14] Indeed, several recent studies have suggested that a large minority of type 2 diabetic patients with CKD suffer progressive loss of renal function without albuminuria. Unfortunately, there are few studies defining nonalbuminuric CKD in diabetes to determine its overlap with classic diabetic nephropathy or with other comorbid disorders or renal biopsy findings.[15–17]

Normal urinary albumin excretion ranges from 1.5–20 μg/min, with microalbuminuria defined as an albumin excretion rate of 20–200 μg/min (30–299 mg/24 h).[5] Of note, urinary albumin excretion decreases by ~25% with sleep or prolonged recumbency. Urinary albumin excretion may be measured in 24-hour urine collections or estimated from random urine albumin/creatinine ratios. In women, the albumin/creatinine ratio is normally <25 mg/g, with microalbuminuria defined either as noted above or, using these sex-specific norms, as a ratio of 25–355 mg/g.[18] Several studies have noted the increased sensitivity of chromatographic methods for the detection of microalbuminuria; however, these newer methods have not gained wide acceptance thus far, with only limited research

TABLE 35-1 Progression of Diabetic Nephropathy and Chronic Kidney Disease

Mogensen Stage[4]	CKD Stage[5]	Clinical or Pathologic Characteristics
I.		Renal hypertrophy and glomerular hyperfiltration
II.	1 (kidney damage* with GFR ≥ 90 mL/min/1.73 m^2)	Glomerular basement membrane widening
III. (incipient DN)	1	Microalbuminuria
IV. (overt DN)	1	Albumin excretin > 300 mg/day
Early	2 (GFR 60–89 mL/min/1.73 m^2)	Fixed proteinuria > 500 mg/day, often nephritic range, hypertension
Intermediate	3 (GFR 30–59 mL/min/1.73 m^2)	Progressive glomerular scarring, nephron loss, worsening hypertension
Advanced	4 (GFR 15–29 mL/min/1.73 m^2)	Progressive glomerular scarring, nephron loss, worsening hypertension
V.	5 (GFR < 15 mL/min/1.73 m^2)	Uremia, ESRD

CKD, Chronic Kidney Disease; DN, Diabetic Nephropathy; GFR, Glomerular Filtration Rate.

*National Kidney Foundation describes kidney damage as either an abnormal renal biopsy finding or a marker of renal damage found on blood, urine, or imaging studies.

use in pregnancy.[19,20] Twenty-four-hour specimens are subject to errors due to undercollection; simultaneous determination of urinary creatinine not only allows estimation of GFR but also provides an index of specimen adequacy, as a complete collection will normally include 10–15 mg creatinine/kg ideal body weight/d.[21] In addition, simultaneous collection of urine for creatinine clearance and microalbumin excretion provides a baseline albumin/creatinine ratio that may increase the accuracy of estimates from subsequent random urine determinations. Unfortunately, albumin excretion may vary significantly from day to day, so several determinations may be required to rule out microalbuminuria.[22]

Recent studies of patients with type 1 diabetes suggest a prevalence of microalbuminuria of 31%–52%; higher prevalence in earlier studies was likely because of patient selection bias. Prevalence of microalbuminuria in type 2 diabetes is 12%–32%, in comparison with 5%–40% in patients with essential hypertension.[23] Challenges in the measurement and interpretation of proteinuria in pregnancy have been reviewed recently.[24]

INTERVENTIONS TO DELAY PROGRESSION OF DIABETIC NEPHROPATHY AND PREVENT CARDIOVASCULAR MORBIDITY

Well-designed prospective trials demonstrated marked decreases in the incidence of DN and other microvascular complications of diabetes with tight glucose control in patients with either type 1 or type 2 diabetes. In the Diabetes Control and Complications Trial (DCCT), there was a 54% reduction in DN when Hemoglobin A1c (HbA1c) was reduced from 9% to 7% in patient with type 1 diabetes.[25] Likewise, the United Kingdom Prospective Diabetic Study (UKPDS) demonstrated a 24%–33% decrease in DN when HbA1c was lowered from 7.9%–7.1% in patients with type 2 diabetes.[26] In this latter study, there did not appear to be a threshold HbA1c associated with risk for DN. Indeed, more recent studies have suggested further improvement in renal outcomes with lower HbA1c targets.[12] Unfortunately, only a minority of patients with diabetes routinely achieve a target HbA1c of <7% in clinical practice.[27]

Several large, well-designed studies have demonstrated the ability of improved BP control to slow the progressive loss of renal function in patients with DN as well as to decrease both microvascular and macrovascular complications and the occurrence of morbid cardiovascular endpoints.[28–30] Interestingly, tight BP control (goal diastolic BP < 85 mmHg, mean achieved BP 144/82, both in excess of current goals) decreased microvascular diabetic complications more so than tight glucose control in the UKPDS.[28] A thoughtful meta-analysis related achieved systolic BP to the rate of decline in GFR (mL/min/y), showing progressively slower renal functional decline with tighter systolic BP control ranging from 180 to 133 mmHg.[30] Further benefits accrue with the use of angiotensin-converting-enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs). For example, captopril decreased the combined endpoint of death, dialysis, or renal transplantation by 50% in patients with type 1 diabetes and overt DN[31]; similar results being observed with other ACE inhibitors.[32] A similar benefit due to ARBs has been demonstrated in patients with type 2 diabetes and overt DN.[33–35] Of note, a careful analysis of clinical and experimental animal data suggests that much of the apparent benefit of ACE inhibitors and ARBs may be due to superior BP control rather than to a BP-independent effect on the glomerulus.[36] Collectively, this literature had led to the wide acceptance of lower BP goals (<130/<80 mmHg) in patients with DN.[37] More recently, reappraisal of clinical trial evidence, particularly the paucity of randomized controlled trials targeting lower BPs or intervention in those with systolic BPs between 130–140 mmHg, has led several groups to temper these recommendations for lower targets in patients with DM, CKD, or DN.[38,39] Even before this recent change, these goals have been difficult to achieve in practice, requiring a median of three separate antihypertensive drugs (including both ACE inhibitors and diuretics) in several clinical trials and being met in only one-tenth to one-fourth of patients in a variety of practice settings.[27,29,30] Beyond patients with DN, meta-analyses of trials in hypertensive patients with nondiabetic renal disease have demonstrated similar benefits of tight BP control in patients with proteinuria, with increased benefit in patients with more severe proteinuria.[5] Similarly, ACE inhibitors (and ARBs) appear to exert a nephroprotective effect, beyond that due to BP control with other agents, in patients with proteinuria. For example, results from the African–American Study of Kidney Disease (AASK) suggested improved renal outcome with BP < 130/80 and therapy with ACE inhibitors in those patients with >220 mg protein/g creatinine at baseline.[40] Likewise, long-term follow-up of patients from the modification of diet in renal disease (MDRD) study demonstrated persisting renal benefit from tight BP control (mean arterial pressure, MAP <92 mmHg) seven years after a four year intervention, in patients with >300 mg proteinuria/d.[41] Taken together, it appears that DN may be representative of other proteinuric renal diseases, in that it is progressive, associated with increased cardiovascular risk, and benefits from tight BP control and treatment with ACE inhibitors or ARBs. As noted above, however, this construct has been questioned recently, due to limited benefit in many patients with progressive nephropathy or improvement in cardiovascular outcomes in several recent trials.[38,42–44]

RENAL ADAPTATION IN WOMEN WITH NORMAL RENAL FUNCTION, DIABETES, DIABETIC NEPHROPATHY, AND NONDIABETIC RENAL DISEASE

Normal pregnancy is characterized by an early 30%–50% increase in GFR, in proportion to increased RPF, that is, filtration fraction is unchanged.[45] Invasive micropuncture studies in gravid rats demonstrate that this gestational hyperfiltration is due to balanced afferent and efferent arteriolar vasodilation without any increase in glomerular capillary pressure. Sophisticated modeling studies suggest that glomerular capillary pressure is similarly normal in human gravidas.[46,47] It now appears likely that these renal functional changes are mediated by a signaling cascade which depends on the ovarian hormone, relaxin, leading to stimulation of endothelin B receptors in the kidney with resulting local synthesis of the vasodilator nitric oxide.[48] GFR then increases progressively, reaching a maximum at 16–20 weeks gestation. Patients with uncomplicated diabetes exhibit similar gestational augmentation in renal function, with increases in GFR of 40%–80% over baseline values[49] by 26–30 weeks. Since GFR is maintained until term but RPF declines somewhat from 29–37 weeks, it appears

that FF increases late in diabetic pregnancy. Most patients with nondiabetic renal disease still exhibit gestational hyperfiltration, sometimes obscuring the diagnosis of underlying CKD. However, as chronic renal insufficiency becomes more advanced, the degree of gestational renal augmentation becomes more variable. It appears striking then that pregnancy increases GFR in only about one-third of women with DN, with the remainder exhibiting either no change in GFR or a loss of renal function as pregnancy progresses.[50,51] Few published studies provide preconception estimates of renal function, most reporting baseline serum creatinine or creatinine clearance data obtained during the first trimester, with follow-up values from the third trimester or postpartum.[52] Whether the fall in GFR can be ascribed to natural or accelerated progression of DN or to the decreased renal function which accompanies preeclampsia[47] remains uncertain. Several small studies suggest that the proportion of women with DN whose GFR falls during pregnancy increases along with baseline serum creatinine (see below).

EFFECTS OF PREGNANCY ON DIABETIC NEPHROPATHY

Physiologic considerations suggest the possibility that pregnancy might profoundly alter the course of DN. However, it is difficult to predict the renal outcomes of these pregnancies from physiologic principles, or even from the changes in renal function observed over the course of gestation.

Several studies have attempted to follow women with DN during and after pregnancy to assess outcomes. These pregnancies often lead to marked increases in proteinuria, which usually resolves following delivery, often returning to prepregnancy levels. Indeed, albuminuria and proteinuria may increase markedly in diabetic women, whether or not they exhibited microalbuminuria before conception.[53,54] By contrast, pathologic albumin excretion is rarely observed in women without diabetes or underlying glomerular disease in the absence of preeclampsia.[55,56] As randomized controlled trials to prospectively assess the effects of pregnancy on the deterioration of renal function in women with DN are impossible, studies have instead focused on (1) Longitudinal (retrospective or prospective) comparison of DN progression in women who have experienced one or more pregnancies. The rates of renal functional loss in the pregnancy group are then compared with those in historical or concurrent control groups who have not been pregnant. (2) Case-control studies comparing the prevalence of DN in diabetic women who have been pregnant with women who have never been pregnant. (3) Studies assessing the effect of parity on the incidence of DN or on its progression to renal failure. These studies all suffer from one or more significant limitations. Most include only a small number of subjects or have relatively limited follow up, given the long course of DN. Many studies accrued or followed patients over a course of several years, failing to account for the impact of strategies (e.g., tight BP control, tight glycemic control, ACE inhibitor use in nonpregnant women, control of hyperlipidemia) generally believed to slow the progression of DN or of associated cardiovascular disease. Importantly, very few studies control for the confounding factors which are known to predict the progression of DN or for preconception renal function and BP control, which appear to predict the impact of pregnancy on the subsequent course of nondiabetic renal disease.

Table 35-2 summarizes the longitudinal studies of pregnant women with DN at baseline.[50,51,57–68] Most of the studies showed no apparent increase in the rate of renal functional loss following pregnancy in women with DN, though pregnancy probably accelerated DN progression toward renal failure in women with more advanced nephropathy at baseline. Kitzmiller et al.[50] assessed renal function in 23 women with type 1 diabetes and overt nephropathy at 9–35 months postpartum. Creatinine clearance decreased in these women at an average rate of 10 mL/min/y, similar to the rates in nonpregnant subjects receiving generally prescribed care during that era. Reece et al.[51] reported on 31 women with diabetes; all had proteinuria during pregnancy with nine women having preexisting overt DN. In these women, and in a second group of 11 women with baseline DN,[59] loss of renal function was similar to that expected in nonpregnant patients. Kimmerle et al.[61] followed 29 women with DN during pregnancy for up to 10 years postpartum without apparent acceleration in the loss of renal function. Rossing et al.[65] compared outcomes in 26 women with baseline DN with those in a control group of 67 women with similar serum creatinine, albuminuria, BP, retinopathy, and other cardiovascular risk factors who did not become pregnant during the 16 years (range 3–28) of follow-up. The rate of decline in creatinine clearance (assessed by the slope of 1/creatinine curves) and progression to ESRD or death were similar in both groups, suggesting that pregnancy has no adverse long-term effect on DN. These authors concluded that renal function deteriorates after pregnancy in women with overt nephropathy, but the rate of deterioration is no different from that expected without pregnancy. By contrast, Gordon et al.[62] reviewed the outcome of 29 patients with DN (defined in their study as >400 mg proteinuria/24 h) at baseline with a mean follow-up of 2.8 years postpartum. Creatinine clearance decreased faster than the expected 10 mL/min/y in 12/28 patients, suggesting the possibility of accelerated progression of DN due to the index pregnancy.

Other studies have suggested that pregnancy may accelerate loss of renal function in women with more advanced DN. Biesenbach et al.[60] studied five women with type 1 diabetes and DN, creatinine clearance <75 mL/min at baseline, and hypertension. Creatinine clearance declined more rapidly than expected, both during pregnancy (22 mL/min/y) and postpartum (17 mL/min/y). Hypertension worsened in all five women during pregnancy, and all had progressed to ESRD within 42 months postpartum. The authors suggested that the accelerated decline in renal function may have been related to worsened hypertension during pregnancy. Similarly, Purdy et al.[63] found that, in patients with moderate to severe nephropathy (10 women with serum creatinine 1.4–1.7 mg/dL and one with serum creatinine 4.1 mg/dL), there was a 40% risk of accelerated, permanent decline in renal function during pregnancy; this would lead to accelerated progression to ESRD, compared with nonpregnant women with nephropathy of comparable severity. Irfan et al.[67] reviewed pregnancy and remote clinical outcomes in 35 women who had DN and a mean serum creatinine of 1.8 (1.4–4.1) mg/dL during the first trimester. In addition, their cohort had a high prevalence of macroscopic proteinuria, hypertension, anemia, retinopathy, and inadequate

TABLE 35-2 Pregnancy and Progression of Diabetic Nephropathy

Citation	Subjects (*n*)	Follow-up (mo)	Accelerated Progression	Progressed to ESRD (*n*)
Kitzmiller, 1981[50]	23	9–35	No	3
Dicker, 1986[57]	5	6–12	No	0
Grenfell, 1986[58]	20	6–120	No	2
Reece, 1988[51]	31	1–86	No	6
Reece, 1990[59]	11	10–45	No	0
Biesenbach, 1992[60]	5*	13–42	Yes	5
Kimerle, 1995[61]	29	4–108	No	8
Gordon, 1996[62]	34	34 (mean)	Yes	3
Purdy, 1996[63]	11*	6–138	Yes	7
Mackie, 1996[64]	6*	6–96	No	3
Kaaja, 1996[68]	6	84 (mean)	No	0
Rossing, 2002[65]	26	36–164	No	5
Bagg, 2003[66]	14	12–192	No	5
Irfan, 2004[67]	35*	6–57	Yes	22

*Serum creatinine ≥1.4 mg/dL or creatinine clearance <75 mL/min at baseline.

diabetic control. The mean serum creatinine increased to 2.5 (1.5–4.2) mg/dL by the third trimester with creatinine clearance remaining stable in 27% of women, worsening transiently in 27%, and demonstrating a permanent decline in 45%. This latter group demonstrated an accelerated progression of DN during pregnancy based on comparison of the slope of their 1/creatinine curves with that observed either before or following pregnancy. Three quarters of all pregnancies were complicated by preeclampsia or worsened hypertension. Sixty-four percent of the total group progressed to dialysis 26 (6–57) months postpartum, mostly attributable to accelerated decline of renal function during pregnancy. By contrast, in another small study, Mackie et al.[64] followed six women with baseline serum creatinine 1.4–2.8 mg/dL for up to eight years postpartum, finding no consistent effect of pregnancy on the progression of DN.

All told, the effect of pregnancy on long-term renal survival in DN appears to parallel that in women with nondiabetic renal disease. In these women, although the incidence of worsened hypertension, superimposed preeclampsia, preterm birth, and intrauterine growth restriction are all high, live births are the norm and renal functional loss is seldom accelerated in women whose baseline serum creatinine is less than 1.4 mg/dL.[3] This similarity in satisfactory outcomes is supported by a report comparing outcomes in women with DN, nondiabetic renal primary renal disease, and renal allograft recipients, all with well-preserved renal function; in these women, hypertension was the best predictor of adverse outcomes during pregnancy.[69] By contrast, several studies of women with more severe renal insufficiency have demonstrated that approximately 30%–40% will suffer irreversible acceleration of renal insufficiency during pregnancy with many of these women progressing rapidly to ESRD[70–72]; further elevations of baseline serum creatinine (>2.5 or 2.8 mg/dL) or uncontrolled hypertension each predict poorer renal and pregnancy outcomes.[73]

Table 35-3 summarizes studies assessing the association of pregnancy with development of DN.[68,74–78]. Miodovnik et al.[74] studied 182 women with type 1 diabetes, 46 with overt DN. All women were treated with intensive insulin therapy throughout pregnancy, and followed for a median of 9.1 (3–16) years postpartum. Of the 136 women without nephropathy at the time of pregnancy, only 13 (10%) eventually progressed to DN, a mean of 10.1 years after the index pregnancy. New proteinuria or poor glycemic control during pregnancy, but not parity *per* se, were each significantly associated with the subsequent development of DN. Of the 46 women with DN at baseline, 12 (26%) progressed to ESRD after a median of six years, unassociated with parity. The overall risk for developing nephropathy was 44% after 27 years of diabetes and the risk of progressing to ESRD was 30% after 10 years of overt DN. Thus, neither pregnancy nor parity appeared to increase either the risk for developing DN in women with type 1 diabetes, or accelerate the progression of DN to renal failure. Kaaja et al.[68] compared the prevalence of DN and its progression in 28 women (six with DN at baseline) with type 1 diabetes, seven years after an index pregnancy, with that in 17 nulliparous controls followed over a similar interval. Neither the development of DN nor its progression appeared to differ between groups. Bagg et al.[66] reported outcomes for 24 pregnancies in 14 women with DN but well-preserved renal function before pregnancy (mean serum creatinine = 0.8 mg/dL). In accord with earlier studies, these pregnancies were complicated by an excess of hypertension and premature delivery, but not by accelerated progression of nephropathy. Nevertheless, 36% of these women had progressed to dialysis a median 7 (3–12) years after the last pregnancy, with

TABLE 35-3 Pregnancy and Development of Diabetic Nephropathy

Citation	Subjects (*n*)	Follow-up (mo)	Increased Risk?	Study Design
Carstensen, 1982[75]	22	7–211	No	Cross sectional
Chaturvedi, 1995[78]	582	NA	No	Cross sectional
Hemachandra, 1995[77]	80	NA	No	Cross sectional
Hemachandra, 1995[77]	30	12 (mean)	No	Case-control
Kaaja, 1996[68]	22	84 (mean)	No	Case-control
Miodovnik, 1996[74]	136	36–193	No	Observational
Miodovnik, 1998[76]	23	14–43	No	Prospective

NA, Not applicable.

additional morbidity and mortality due to retinopathy, coronary-, cerebral-, and peripheral vascular disease. These authors remind us that, even when short-term outcomes are good, we must counsel our patients regarding the morbid natural history of diabetic nephropathy and CKD.

Carstensen et al.[75] performed a cross-sectional study of 22 pairs of women with type 1 diabetes matched by age and duration of the disease, comparing the prevalence of microvascular complications in women who had never completed a pregnancy with those who had completed one or two pregnancies. They observed no differences in outcome up to 17.7 years after the birth of the oldest child and up to 24 years after the onset of diabetes. Similarly, Miodovnik et al.[76] prospectively compared 23 pregnant and 23 nonpregnant women with type 1 diabetes without evidence of microvascular disease at baseline. All women were managed identically during the 9-month pregnancy period (or a comparable control period in the nonpregnant women). None of the women progressed to DN during the subsequent two years of prospective follow-up, suggesting that pregnancy does not precipitate the development of DN. Likewise, Hemachandra et al.[77] compared the prevalence of microvascular complications in 80 pairs of women, either parous or nulliparous, all with type 1 diabetes of similar duration and matched for age and ethnicity. They found no differences in microvascular outcomes between the two groups. They also followed a subgroup of 30 primiparous women for a mean of 11.8 months postpartum, matched to a group of 30 nulliparous women followed for the same period. As in the study by Miodovnik et al.,[76] there were no differences between the two groups in the postpartum incidence of DN.

Chaturvedi et al.[78] performed a cross-sectional study examining the prevalence of microalbuminuria and macroalbuminuria in 776 nulliparous women with type 1 diabetes compared with 582 parous women with type 1 diabetes (352 with a single pregnancy and 229 with two or more). After adjusting for age and duration of the disease, there were no significant differences between groups with respect to the presence of microalbuminuria, whereas the prevalence of macroalbuminuria was actually lower in parous women (6%) than in nulliparous women (10%).

In summary, most of the available studies suggest that pregnancy is not associated with development of nephropathy or with accelerated progression of preexisting nephropathy, especially when renal function is well-preserved. However, some limited data suggest that, as in women with more advanced nondiabetic renal disease, pregnancy may accelerate the loss of renal function and progression to ESRD when GFR is decreased before pregnancy.

EFFECTS OF DIABETIC NEPHROPATHY ON PREGNANCY OUTCOME

Pregnancy outcomes are worse in women with DN than in those with uncomplicated diabetes. This appears due to: (1) the increased incidence and severity of hypertensive disorders of pregnancy, (2) increased prematurity due to early delivery in the setting of poorly controlled hypertension or severe preeclampsia, and (3) the increased risk of fetal growth restriction and fetal distress. Since the incidence of preeclampsia is increased in women with insulin resistance,[79] diabetes alone (without nephropathy, 10%–20%), or chronic essential hypertension (20%–40%), it is not surprising that there is enhanced risk to women with DN whose condition may include all of these abnormalities. Outcomes appear to be worst in those women with more advanced renal insufficiency and less well-controlled hypertension at baseline, as is the case in women with nondiabetic renal disease.[70–72] Table 35-4 summarizes rates of selected perinatal complications in women with DN.[50–52,58,61,62,69,80–84]

Many women with diabetic nephropathy have preexisting chronic hypertension, and even in those who do not, perinatal complications are frequently associated with hypertension, often severe, that develops during pregnancy. Preeclampsia or superimposed preeclampsia in the setting of underlying hypertension are common complications of DN. That granted, women with DN, many of whom have hypertension, proteinuria, and renal insufficiency at baseline, have all the features which make the clinical diagnosis of preeclampsia uncertain, both in practice and in outcomes research.[85] These diagnostic difficulties may contribute to some of the variability in reported rates of preeclampsia in studies of women with DN, as shown in Table 35-4. Importantly, they make it difficult for clinicians to accurately diagnose preeclampsia and weigh the risks of expectant management versus early delivery in the setting of worsened hypertension, proteinuria, and renal function.

TABLE 35-4 Pregnancy Outcomes in Diabetic Nephropathy

Citation	Subjects (*N*)	HTN	PE	PNM	IUGR	Delivery <34 wks	Delivery 34–36 wk	Delivery >36 wk
Kitzmiller[50]	26	31%	15%	11%	21%	31%	41%	28%
Grenfell[58]	22	NA	NA	0%	14%	27%	23%	50%
Reece[51]	31	23%	35%	6%	16%	23%	32%	45%
Pierce[81]	39	NA	NA	3%	10%	26%	23%	51%
Gordon[62]	45	27%	53%	0%	11%	16%	35%	49%
Kimmerle[61]	36	61%	19%	0%	22%	31%	NA	NA
Rosenn[82]	61	47%	51%	6%	11%	25%	28%	47%
Reece[80]	27	77%	53%	4%	9%	26%*	0	74%
Bar[69]	24	46%	46%	4%	21	NA	17%**	NA
Khoury[52]	39[a]	NA	41%	5%	8%	7%***	NA	NA
	12[b]	NA	33%	0%	8%	17%***	NA	NA
	9[c]	NA	44%	11%	33%	44%	NA	**NA**
Hopp[83]	76	NA	71%	9%	39%	NA	NA	NA
Young[84]	11	18%	64%	0%	40%	NA	64**	NA

HTN, chronic hypertension; PE, preeclampsia; PNM, perinatal mortality; IUGR, intrauterine growth restriction; NA, not available.
#36 wk,**<37,***<32 wk.
[a]Patients with baseline creatinine #1.0 mg/dL.
[b]Patients with baseline creatinine >1.0 to 1.5 mg/dL.
[c]Patients with baseline creatinine >1.5 mg/dL.

There has been an explosion of research elucidating mechanisms which lead to hypertension and to proteinuria in women with preeclampsia.[47,48] It is now clear that proteinuria and the glomerular pathology which is most characteristic or preeclampsia both result from a relative deficiency of the angiogenic factors, vascular endothelial growth factor (VEGF) and placental growth factor, which are scavenged by pathologically-elevated levels of a soluble VEGF receptor. It is clear that similar mechanisms take place in the setting of underlying DN and that measurement of (anti-)angiogenic factors may be useful in differential diagnosis or risk stratification of women with apparent preeclampsia diagnosed by clinical criteria, alone[86,87]; by contrast, it is unclear how pathologic regulation of these angiogenic factors might interact with microvascular abnormalities, such as proliferative retinopathy, in women with diabetes. Similarly, vasoconstriction, hypertension, and oxidative stress in preeclampsia appear due to increased signaling at angiotensin (AT_1) receptors due to autoantibodies which mimic the effects of angiotensin II.[88] Given the key role of the renin-angiotensin system in progression of DN, it will be crucial to define this mechanism in women with DN and to seek therapies which can reverse this pathophysiology without harming the fetus.

Few studies have examined the association of microalbuminuria and perinatal outcome. Combs et al.[89] found that even women with total protein excretion in the microalbuminuric range (<500 mg total protein per 24 hours) have an increased risk of developing preeclampsia. Risk increased dramatically (from 10%–40%) when proteinuria exceeded 190 mg/d, but preeclampsia did not appear more likely with further increases in proteinuria. Similarly, Ekbom et al.[90] found that the rate of prematurity among women with microalbuminuria was significantly increased, primarily due to an increased incidence of preeclampsia in this subpopulation. By contrast, another study failed to detect this increased risk of preeclampsia in women with 190–499 mg proteinuria, though it may have differed significantly in patient characteristics, case definitions for the diagnosis of preeclampsia, and laboratory methods.[91] When DN progresses to overt nephropathy with macroproteinuria, there does not appear to be any further effect of the magnitude of proteinuria on pregnancy outcome, save for rare cases of refractory edema, hypoalbuminemia, and their morbid consequences. Khoury et al.[52] reported that very-low-birth weight and neonatal hypoglycemia (in women with type 1 diabetes) were significantly associated with high baseline serum creatinine, independent of proteinuria and glycemic control. Decreased renal function also predicted a trend toward increased rates of perinatal death, growth restriction, and respiratory distress syndrome in that study.

Uncontrolled hypertension before conception or inadequately controlled hypertension early in pregnancy can predict maternal morbidity and poor pregnancy outcomes in women with nondiabetic renal disease. As discussed earlier, tight BP control is likely renoprotective in nonpregnant women with DN. There are few studies to determine whether we should similarly target tight BP control early in pregnancies complicated by DN. In a

compelling preliminary report, Carr and colleagues[92] followed 43 gravidas with DN comparing outcomes in those women who achieved a target MAP <100 mmHg before 20 weeks gestation with those who did not. The women with poorer BP control exhibited greater proteinuria, a fivefold increase in the likelihood of developing nephrotic syndrome, and a 13-fold increase in the likelihood of delivering before 32 weeks. This report may be viewed as complementary to the results of several studies which suggest that tight BP control with ACE inhibitors before conception limits proteinuria, improves pregnancy outcome, and may exert a persisting nephroprotective effect, even when these drugs are discontinued at the diagnosis of pregnancy.[93] Clinicians have been hesitant to treat women of childbearing age using ACE inhibitors following a 2006 report, which identified a 2.7-fold increase in congenital malformations, due entirely to increases in cardiovascular and central nervous system malformations[94] following ACE-inhibitor exposures limited to the first trimester. Subsequently, several much larger studies have failed to confirm concerns regarding first trimester exposure,[95–98] some suggesting that any increased risks of malformation may be related to maternal hypertension or to undiagnosed diabetes, rather than its treatment. Likewise, secondary analysis of 208 pregnancies which occurred during a randomized clinical trial of candesartan in type 1 diabetics suggested no excess risk due to first trimester ARB exposure.[99] So, although it seems prudent to discontinue their use when pregnancy is first confirmed, and many may argue against their use in women with prepregnancy essential hypertension, due to the high rates of unintended pregnancy and of delayed or limited antenatal care, these risks must be weighed against the significant potential benefits of their use in women of childbearing potential with compelling indications, such as those with underlying diabetic nephropathy. However, even these women should be counseled specifically to seek obstetric care early following conception and to discontinue these drugs to avoid the fetopathy which results from exposures following the first trimester.[100,101] Here we also note that many clinicians similarly deny ACE-inhibitor therapy to postpartum nursing mothers with DN out of a mistaken belief that neonatal drug exposure might prove damaging. In fact, captopril has been shown clearly not to be excreted in milk and infant exposure is undetectable.[102,103] with similarly reassuring data for enalapril and quinapril.[104,105]

Fetal outcome is often affected by prematurity as a result of deteriorating maternal status requiring early delivery, and also due to an increased risk of fetal growth restriction and fetal hypoxia. Worsening nephropathy and superimposed preeclampsia appear to be the most significant risk factors associated with fetal distress, whereas hypertension and decreased creatinine clearance are the strongest predictors of fetal growth restriction. As shown in Table 35-4, perinatal survival of infants born to mothers with DN has been uniformly excellent in recent years. However, increased prematurity in pregnancies complicated by DN predicts an increased risk of developmental and functional problems in the children born of these pregnancies. Indeed, Kimmerle et al. followed 36 infants of mothers with DN for 0.5–11 years after delivery, and found that five had severe psychomotor impairment, and three had mild developmental impairment, primarily associated with prematurity.[61] Thus, although women with DN may usually expect to deliver a viable fetus and take home a reasonably healthy infant, this group of patients is the one most likely to have a complicated course of pregnancy, requiring expert care and intensive management.

SUMMARY

The striking renal and cardiovascular adaptations that characterize normal pregnancy may interact with the pathophysiologic mechanisms which underlie nephropathy in women with diabetes. Although the literature includes excellent studies focusing on the relationship of glycemic control and microvascular complications in patients with the disease, there are shamefully few prospective studies addressing the effects of pregnancy or seeking to define optimal management before and during pregnancy on the course of DN and its complications. Research, which might directly impact care of women with DN, needs to include (1) clearer definitions of the duration of intensive preconception control of glucose, BP, and proteinuria required to improve pregnancy outcomes, (2) determining whether tight BP control during pregnancy will improve maternal and fetal outcomes without exacerbating fetal growth restriction, (3) assessing whether the choice of antihypertensive agents used in gravidas with DN should differ from those used in women with chronic hypertension, and, (4) determining how best to use (anti-) angiogenic biomarkers related to the pathophysiology of preeclampsia to allow early and accurate differentiation of superimposed preeclampsia from worsened hypertension and proteinuria due to DN alone.

Although it is difficult to determine with certainty the long-term effects of pregnancy on the progression of DN, it appears that pregnancy neither precipitates DN nor accelerates its progression in women with near-normal renal function and well-controlled BP. Tight BP control before and throughout pregnancy may improve both pregnancy outcomes and long-term renal prognosis in women with DN. Further, women would benefit if their glycemic and BP control were both optimized before pregnancy is contemplated, using ACE inhibitors up until pregnancy is confirmed.

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Fetal Lung Maturation in Pregnancies Complicated by Maternal Diabetes

36

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Time is a dressmaker specializing in alterations.

—Faith Baldwin

Key Points

- Appearance of phosphatidylglycerol is delayed in diabetic pregnancies with and without adequate glucose control
- Normalization of maternal glucose values allows lung maturity to progress at a rate similar to nondiabetic pregnancies
- In the presence of accurate obstetrical dating and good maternal glucose control, amniotic fluid assessment for fetal lung maturity prior to elective delivery at term is not needed
- With uncertain obstetrical dates or poor glucose control, amniocentesis is recommended before elective term delivery prior to 39 weeks

Respiratory distress syndrome (RDS), a deficiency in surfactant in premature infants leading to increased surface tension within alveoli, subsequent alveolar collapse, and difficult gas exchange, which then leads to neonatal hypoxia, has been historically one of the major complications of neonates born to mothers with diabetes. In the 1970s, an estimated 31% of newborns from diabetic pregnancies were complicated by RDS; this rate has been reduced currently to less than 3% with improved glycemic control and improved understanding of fetal lung maturity.[1]

FETAL LUNG MATURATION

The pulmonary system begins development at approximately three weeks after conception, but it is at approximately 16–20 weeks of gestation that the development of early bronchioles and vascularization of pulmonary epithelium occurs.[2] At 22–23 weeks of gestation, alveolar development occurs with proliferation of capillaries around these alveoli to allow for effective gas exchange. Alveoli are lined with type II pneumocytes that produce phospholipids packaged in lamellar bodies. Surfactants are a type of phospholipid that facilitates alveolar expansion upon neonatal respiratory efforts.[3] These surface-active compounds reduce surface tension within the alveolar sacs, allowing them to expand with less pressure during the initial respirations following delivery. In the absence of surfactant, much higher ventilatory pressures are required to expand the alveoli. If the pressures required exceed what the newborn can generate, positive pressure ventilation may be required for initial alveolar inflation and adequate gas exchange.[3] In the third trimester of pregnancy, owing to the outflux of fetal respiratory secretions, surfactant is found in the amniotic fluid, which can be assessed to determine lung maturity.

FETAL LUNG MATURITY TESTS

Currently, there are biochemical tests that measure concentrations of pulmonary surfactant or biophysical tests that measure surface-active effects of these phospholipids in the amniotic fluid.[2]

Fluorescence polarization is based on the ratio of surfactant to albumin in amniotic fluid to predict lung maturity.[3,4] It is a simple automated technique with excellent validity that can be performed in less than an hour. The amount of sample needed is only 1 mL. In a retrospective study conducted by Fantz et al., 15 samples from women whose neonates developed RDS and 170 controls, a value of ≥ 45 mg/g had a sensitivity of 100 (95% CI of 82–100) and specificity of 90% (95% CI of 78–89) for diagnosing surfactant-deficient RDS.[4] Women who received corticosteroids were excluded.[4] Since this test relies on a ratio of surfactant to albumin, interpretation of the results from fluorescence polarization is affected by both meconium and blood.[3]

Lecithin to sphingomyelin ratio measures these two surfactants in amniotic fluid. Gluck et al. subjected amniotic fluid from a spectrum of gestational ages to thin layer chromatography and found that sphingomyelin rose early in the third trimester, but returned to baseline as term approached.[5–7] In contrast, lecithin began to rise at the same gestational age, but continued to rise throughout gestation with a sharper increase as term approached (Figure 36-1). In normal pregnancies, a

cutoff ratio of twice as much lecithin as sphingomyelin was identified as an assurance of fetal maturity (lecithin–sphingomyelin [L/S] ratio ≥2:1).[8,9] Reliability of predicting pulmonary maturity was found to be excellent for nondiabetic pregnancies using this cutoff.[7] However, amniotic fluid and blood interfere with interpretation of the test. This test has fallen out of favor as newer tests have emerged, as trained personnel are needed to conduct the test, an average of five to six hours is required to run the test, and blood and meconium interfere with results.[2]

Soon after discovery and utilization of the L/S ratio, there was concern that a ratio of 2:1 may not be as predictive of maturity in pregnancies complicated by maternal diabetes. In one study, up to 28% of infants of diabetic mothers with an L/S ratio ≥2 were reported to have respiratory insufficiency.[10] Cunningham et al. found RDS in 6 of 29 (20.7%) infants of diabetic mothers delivered at 34–37 weeks after a mature L/S ratio.[11] In other populations, the L/S ratio was reported to be just as predictive in diabetic mothers as in nondiabetics.[12] Regardless, a more predictive test was clearly needed to assure pulmonary maturity in pregnancies complicated by maternal diabetes.

Phosphatidylglycerol (PG) is one of the last surfactant components to appear in pulmonary secretions because it enhances spread of phospholipids in the alveolar surface.[2] An absolute concentration cutoff (0.5 µg/mL) using chromatography was established to predict pulmonary maturity (PG+). The presence of PG was found to be an excellent predictor of pulmonary maturity in both normal and diabetic pregnancies.[11–13] The predictive value of a positive PG was reported as 98%–100% in both diabetic and nondiabetic pregnancies.[14,15] Unfortunately, the absence of PG was even less predictive of RDS than an immature L/S ratio. Indeed, most pregnancies without detectable PG near term had no evidence of clinical pulmonary immaturity. Rates of RDS with negative PG were only 16.7% in diabetic and 14.4% in nondiabetic pregnancies.[14] Currently, PG can be assessed with a slide agglutination test using antisera specific for PG and this test is not affected by blood or meconium.[2]

Lastly, recently there has been a new test, lamellar body count, that has been used to identify lung maturity. In type II pneumocytes, surfactant is stored in lamellar bodies. These are then secreted into the alveolar space and, therefore, found in amniotic fluid. A standard hematologic counter can be used to measure lamellar bodies as they have similar size to platelets. In a prospective trial of 80 patients ranging in gestational age from 28 to 40 weeks of gestation, a lamellar body count of 50,000 uL predicted fetal lung maturity with a sensitivity of 85% and specificity of 70% for the prediction of RDS.[16] In 90 pregnancies complicated by type 1 diabetes, a lamellar count of >37,000/uL had a sensitivity of 80% and specifity of 100% in the prediction of fetal lung maturity when compared to PG and L/S ratio and there were no cases of RDS.[17]

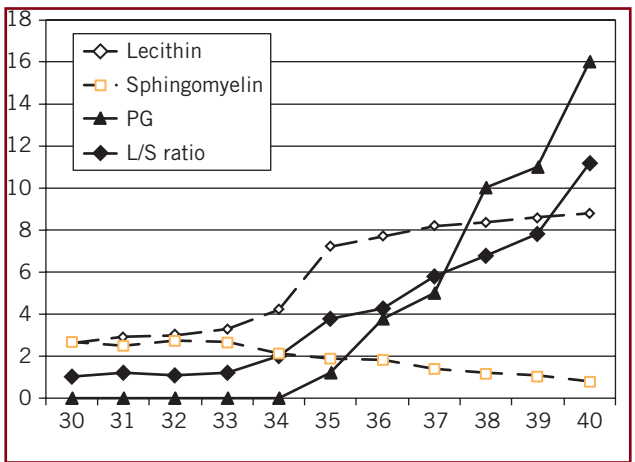

Figure 36.1 Appearance of surfactant components in the amniotic fluid by gestational age. Adapted from data in References.[3–5] Lecithin and sphingomyelin concentrations are displayed in mg/dL, PG is displayed as percentage of total phospholipids, and the L/S ratio is displayed as the result of that calculation (2 is 2:1 ratio).

FACTORS INFLUENCING FETAL LUNG MATURATION IN DIABETIC PREGNANCIES

The increased risk of RDS in diabetic pregnancies could be due to delay in production of alveolar phospholipids or abnormal pulmonary function. As mentioned above, the proportion of diabetic pregnancies with delayed appearance of a mature L/S ratio or a positive PG varied greatly between populations studied. Ojomo and Coustan reported that PG was absent in a significant proportion of pregnancies complicated by diabetes at term gestations (26% at 37 weeks, 20% at 38 weeks, and 4% at 39 weeks).[18] The highest percentage with absent PG occurred in overt diabetes as compared to gestational diabetes. Tsai et al. likewise found delayed appearance of PG in their pregestational diabetics (Class B-RF) but not in gestational diabetic pregnancies at term; they did identify a delay in PG positivity in gestational diabetics below 37 weeks as compared to controls.[19] Glycemic control has also been implicated to play a role. Kulovich and Gluck also found a clear delay in the onset of PG presence in poorly controlled gestational diabetics but not in other classes of diabetes.[13] Landon et al. found that regardless of diabetes type, fetal lung maturity occurred later in pregnancies with poor glycemic control (mean plasma glucose level >110 mg/dL) and when infants were stratified by maternal plasma glucose levels.[20] Similarly, Moore in a case–control study involving 295 pregnancies complicated by diabetes demonstrated no differences in the rate of rise of the amniotic fluid L/S ratio among types of diabetes or degree of glucose control.[21] However, amniotic fluid PG was delayed approximately 1.5 weeks among women with diabetes (either pregestational or gestational diabetes mellitus [GDM]) compared to controls (Figure 36-2) and was associated with earlier and higher peak in phosphatidyl inositol.[21] It may be that elevated maternal plasma levels of myoinositol in pregnancies complicated by diabetes may inhibit or delay the production of PG in their fetuses.[21]

IMPACT OF MATERNAL DIABETES ON NEONATAL RESPIRATORY DISTRESS SYNDROME

Although biochemical changes appear to play an important role in the development of RDS in pregnancies complicated by diabetes, there may also be physiologic etiologies. Kjos et al. reviewed 526 diabetic pregnancies delivered within five days of amniotic fluid

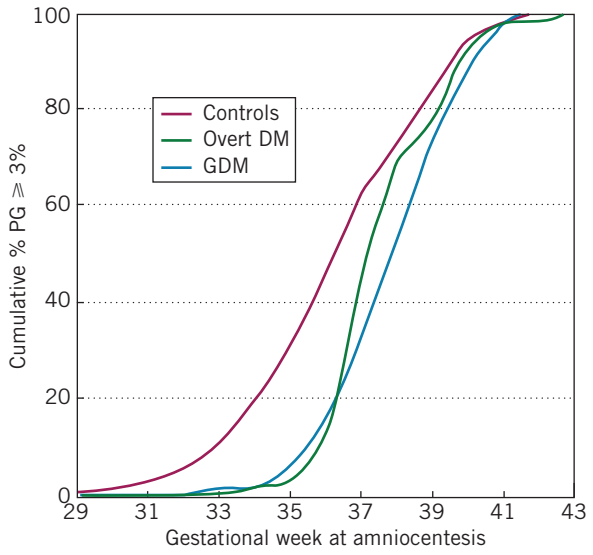

Figure 36.2 Delay in fetal pulmonary phosphatidylglycerol was associated with a sustained peak in phosphtidyl inositol in diabetic pregnancy. (Moore[21]).

assessment for lung maturity. RDS was noted in 3.4% of infants, and (1%) had surfactant deficient RDS. All five infants with surfactant-deficient RDS were delivered prior to 34 weeks and had immature PG and L/S results.[22] Transient tachypnea, hypertrophic cardiomyopathy, and pneumonia led to RDS in majority of infants all of which were delivered by cesarean section and had mature L/S ratios.[22] They concluded that surfactant-deficient RDS is not a problem in well-managed diabetic pregnancies beyond 34 weeks and thus amniotic fluid testing for fetal lung maturity is unnecessary.[22]

In a follow-up study, Kjos et al. compared a cohort of 1457 diabetic women with well-dated pregnancies, who were delivered at term without pulmonary maturity testing to a historical comparison group of 713 women delivered after the assessment of pulmonary maturity.[23] There were no differences in rates of surfactant-deficient RDS between those delivered without amniocentesis and those delivered after amniocentesis (0.8% vs. 1.0%). Transient tachypnea likewise did not differ between groups (1.3% vs. 0.8%). The main risk factor for respiratory compromise was cesarean delivery (OR 2.21 [2.04–2.27]). They concluded that routine fetal lung maturity testing is unnecessary in well-dated diabetic pregnancies and should be abandoned. Furthermore, the study conducted by Moore demonstrated that the average gestational age that a nondiabetic fetus achieves pulmonary maturity is 34–35 weeks of gestation, furthermore more than 99% of normal newborns have a mature phospholipid profile by 37 weeks. In pregnancies complicated by diabetes, however, lung maturity occurs approximately 10 days after the nondiabetic pregnancies (38.5 gestational weeks). Delivery prior to 38.5 weeks of gestation, unless indicated by urgent fetal and maternal indications, should be preceded by documentation of pulmonary maturity by amniocentesis.

SUMMARY

The near-term infant of a mother with poorly controlled diabetes is more likely to have neonatal respiratory dysfunction than is the baby of a nondiabetic mother. In general, the same thresholds and tests used for fetal lung maturation can be used to predict a low risk of RDS in pregnancies with gestational and pregestational diabetes. The combination of accurate dates and more strict glucose control has led to a recent decline in the use of amniotic fluid assessment for fetal lung maturity. In well-dated term diabetic pregnancies with adequate glucose control, there is no need for amniocentesis for fetal lung maturity testing. In the absence of either early confirmation of dates or adequate glucose control, amniocentesis for lung maturity testing is still indicated if delivery is planned before 39 weeks.

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Timing and Mode of Delivery

37

Oded Langer, MD, PhD

Information is a beacon, a cudgel, an olive branch, a deterrent, depending on who wields it and how…

—Steven D. Levitt

Key Points

- The timing of delivery of the diabetic patient is a balancing act between potential intrauterine death, shoulder dystocia, and the consequences of premature delivery.
- Achieving targeted levels of glycemic control will reduce rates of fetal demise.
- Stillbirths are not limited to late third trimester; therefore, the care provider needs to be vigilant to level of glycemic control and fetal surveillance testing.
- For diabetic women in poor glycemic control, regardless of gestational age, lung maturity testing should be performed.
- For diabetic women in good glycemic control and reassuring dates after completing 37 weeks' gestation, delivery can be performed without prior lung testing.
- In diabetic pregnancies, the majority of shoulder cases occur in fetuses >4000 g (84%); 58% in nondiabetic pregnancies.
- Achieving glycemic control will decrease macrosomia and the subsequent shoulder dystocia rates.
- For nondiabetic women, trial of vaginal delivery with estimated fetal weight (EFW) ≥4000 g should be considered; liberal policy toward cesarean section is a consideration in the presence of labor abnormalities.
- For diabetic patients, elective cesarean section delivery is strongly recommended when EFW4000–4250 g; the decision may be individualized in this weight range.
- The price of neonatal life and permanent perinatal morbidity cannot be balanced against a higher cesarean section rate.

INTRODUCTION

The care provider's decision on the optimum time to deliver the infant in the pregnancy complicated by diabetes needs to balance between the perceived risk of late intrauterine death and shoulder dystocia and the consequences of unnecessary prematurity and cesarean section delivery. The timing of delivery will be mandated by the risk ratio of removing the fetus from the intrauterine environment compared to the risk to the mother and the fetus because of the intervention. Therefore, there is no absolute benefit for both patients. The benefit to one may result in increased risk for the other. As a rule of thumb, this equation is heavily weighted toward fetal versus maternal perspective. The maternal preconditions for planned delivery are integrally involved with the potential for damage to the fetus. For example, the failure of the mother to achieve the established levels of glycemic control may cause hyperinsulinemia in her fetus. The indications for planned delivery of a diabetic patient include macrosomia/large-for-gestational age (LGA), previous stillbirth, prevention of fetal demise, presence of hypertensive disorders, diabetic vasculopathy, poor compliance to the diabetic protocol resulting in adverse glycemic control, and reduction in potential shoulder dystocia.[1]

FACTORS ASSOCIATED WITH FETAL DEMISE: LGA AND GLYCEMIC CONTROL

Fetal demise, excluding congenital anomalies, is associated with the level of glycemic control and the vascular complications in the pregnant diabetic woman. A brief review of the literature[2,3] reveals that approximately15%–25% of fetal death in the general population is due to diabetes in pregnancy. Today, our knowledge regarding the causes of diabetic death has expanded, but still, in certain cases, the origins are not clear. However, the high stillbirth rate (three- to fourfolds higher than the general population) indicates that diabetes per se is in large part responsible for the high rate. In a study examining the relationship between stillbirth rate and level of glycemia, 93 cases were involved, that is, 59 type 1 and 34 with type 2 diabetes. There were 73 stillbirths, 12 early neonatal deaths, 8 late neonatal deaths, and 18 attributable to congenital malformations. Sixty four of the cases were explained by antepartum asphyxia, four to intrapartum asphyxia, and three to postnatal hyaline membrane disease; only two were attributable to postnatal infection. The study provided evidence that maternal hyperglycemia not only causes fetal macrosomia but also angiopathy affecting the uteroplacental blood vessels and consequent

fetal hypoxia.[4] In pregnant diabetic women, Brownlee[5] suggested that hyperglycemia induces intracellular production of advanced glycation end-product precursors that are responsible for damage to vascular endothelial cells. It is through this pathway that hyperglycemia activates protein kinase C (PKC); PKC decreases the expression of endothelial nitric oxide synthase and upregulates endothelin-1 that stimulates blood flow abnormalities. PKC also increases vascular endothelial growth factor, changing vascular permeability and increasing transforming growth factor β that leads to capillary occlusion. Animal models have suggested other possible mechanisms. Abnormalities in fetal apoptosis have been proposed. Diabetic embryopathy may be the result of an increased production of free radicals.[6] Vasoactive agents such as endothelin-1 and prostaglandin E2 are raised in pregnancy affected by diabetes and may be related to induction of placental insufficiency and fetal hypoxia.[7]

Consequently, it is not realistic to expect that all deaths can be prevented with the currently available tools for fetal surveillance and management protocols.[8,9] Current data suggest that fetal demise in the third trimester remains a major contemporary perinatal concern. Studies of type 1,[10] type 2,[11] and gestational diabetic mellitus (GDM)[12] pregnant diabetic women reported statistically significant increased risk for fetal mortality among these women in comparison to nondiabetic controls. Fewer than 10% of the stillborns had recognizable anomalies. Therefore, maternal diabetes and failure to achieve glycemic control may cause higher rates of fetal demise than congenital anomalies.

Fetal demise in the pregnant diabetic woman is often described as "unexplained fetal death." The demise is the result of the metabolic acidosis developed in the fetal compartment in the presence of an abnormal glucose level rather than the traditional explanation of fetal hypoxia. During the second and up to the middle of the third trimester, the risk for fetal demise is not as pronounced as during late gestation; the rates increase as the fetus's affinity to insulin is enhanced. Although insulin can be detected as early as the first trimester, the affinity to insulin action becomes significant at approximately 26–28 weeks' gestation. This results in fetal hyperinsulinemia leading to fetal acidemia and hyperlacticemia often without evidence of fetal hypoxia. Supporting this concept, the work of Pettitt et al.[13] in Pima Indians found that in 236/1000 fetal deaths, the majority occurred in LGA infants of GDM mothers. Needless to say, fetal hypoxemia and acidemia can occur in all types of diabetes, especially pregnancies associated with hypertensive disorder and microvascular complications (types 1 and 2). Maternal hyperinsulinemia alone can be a cause for vasoconstriction leading to fetal hypoxia.[14] Our data on 1004 preexisting diabetic women (358 type 1 and 746 type 2) demonstrated that 73% of stillbirths and 72% of neonatal deaths were LGA infants. In contrast, in 4757 GDM patients, only 27% of stillbirths and 28% of neonatal deaths were LGA. Overall deviant fetal growth, LGA and small-for-gestational age (SGA), was found in 61% of the stillbirths and 42% of the neonatal deaths. During the same period, the LGA rate in nondiabetic patients was approximately 12% in our population. In preexisting and gestational diabetes 85% and 67%, respectively, did not achieved targeted levels of glycemic control.[15,16] During the same period, in nondiabetic patients, the rate of perinatal mortality for LGA fetuses was approximately 11% (Table 37-1).

TIMING OF DELIVERY: GESTATIONAL AGE

The view that the fetus of the mother with diabetes matures early and reaches the equivalent of term by 36 weeks gestation was championed by Peel and Oakley of King's College Hospital, London, in the late 1940s. They delivered all babies at 36 weeks based on a protocol that was diligent to the control of the mother's diabetes during pregnancy. The key outcome parameter they

TABLE 37-1 Selected Characteristics of Patients with Diabetes Complicated with Perinatal Mortality

	Stillbirth		Neonatal Death		
	PGDM	GDM	PGDM	GDM	Nondiabetic
Nulliparity (%)	28%	26%	32%	13%	26.1%
Poorly controlled	85%	65%	87%	72%	—
LGA	73%	27%	72%	28%	11%
AGA	21%	39%	22%	58%	78%
SGA	5%	34%	6%	14%	11%
Obesity	50%	50%	48%	50%	24%
History of previous stillbirth	17%	19%	16%	13%	1.5%
Hx of macrosomia	52%	45%	49%	40%	8%
Preeclampsia	12%	10%	13%	8%	5.0%
Chronic hypertension	22%	22%	27%	23%	6.1%

GDM, Gestational diabetes mellitus; PGDM, pregestational diabetes mellitus Type 1 and Type 2; AGA, appropriate-for-gestational age.

failed to address was the rise in neonatal death from 10.7% to 14.2%.[17] White et al.[18] in Boston also recommended that women with Class D, E, and F diabetes be delivered at 36 weeks, although they did allow Class B and C to reach 38 weeks and Class A to go to term. In 1979, Roversi et al.[19] challenged this regimen demonstrating that it was meticulous attention to blood glucose control that was the key factor in reducing perinatal mortality and, in particular, late intrauterine fetal death. Using the maximum dose of insulin that could be tolerated by the mother, they carried 94% of the pregnancies to 38 weeks or more, 10% not being delivered until after 40 weeks. The only late fetal death occurred at 37 weeks in a woman with diabetic nephropathy. Drury et al.[20] at the National Maternity Hospital in Dublin reported their experience of the first 141 diabetic pregnancies managed using a regimen of tight control and not delivering the baby before full term irrespective of the degree of severity of the diabetes unless obstetric complications necessitated intervention. This was done without the use of either cardiographic surveillance or ultrasonic assessment of fetal well-being. Spontaneous labor ensued in 57% of cases; the cesarean section rate was 20% and perinatal mortality 31/1000.

Varied suggested times of delivery have been reported in the literature. However, this multidimensional issue must be attentive to deviant fetal growth, level of glycemic control, lung maturation, and fetal metabolism. The continuing controversy about the optimal timing of delivery for women with GDM weighs the risk of stillbirth against that of neonatal and infant morbidity and mortality. In Rosenstein's study,[21] the mortality risk of a week of expectant management was defined as the risk of stillbirth versus that week plus the mortality risk experienced by infants born in the following week of gestation. Their report was based on a data set of 4,190,953 deliveries (excluding congenital anomalies) but including GDM from gestational ages 36–42 weeks. They reported that at 36–39 weeks' gestation, women with GDM had statistically significant relative risk (RR) of stillbirth (approximately 1.45). The risk of mortality from delivery is higher than expectant management at 36 weeks' gestation but similar at 37 weeks. In contrast, expectant management exceeds the risk of delivery at ≥38 weeks. The problem with this study is the use of an administrative database lacking vital data required to draw adequate conclusions such as information on glycemic control, treatment modality, and stratification of neonatal outcome such as macrosomia. In our data, 70% of stillbirths of type 2 diabetic occurred after 37 weeks' gestation and 30% to type 1 women. Of the neonatal deaths in preexisting diabetes, 90% occurred after 37 weeks. Different associations to gestational age were found in the GDM patients in whom 62% of stillbirths and 43% of neonatal deaths occurred before 37 weeks. The majority of these neonates (82%) died within a week after delivery reflecting the severity of the neonatal disease.[15,16]

The current data suggest that the majority of stillbirths and neonatal deaths are the result of patients' failure to achieve glycemic control, and metabolically impaired LGA infants (not excluding SGA). These data support planned intervention for delivery. On the other hand, the distribution of stillbirths throughout the third trimester challenges the recommendations of experts to initiate fetal testing in GDM late in the third trimester as over 62% of stillbirths in this group occur below 37 weeks' gestation.

LUNG MATURATION AND IATROGENIC PREMATURITY

As described above, the fear of stillbirths in the past and even in current practice in many maternity units in the United States and Europe encouraged the policy of planned delivery of diabetic patients at approximately 34–37 weeks' gestation. This policy significantly decreased the stillbirth rate but, in contrast, resulted in iatrogenic prematurity with the accompanying neonatal complications especially respiratory distress syndrome (RDS) (formerly known as hyaline membranous disease). These complications encouraged research in the development of fetal maturity lung testing, which is addressed at length elsewhere in the book.

In the past few decades, lung maturity testing has enabled us to significantly decrease iatrogenic prematurity and to comprehend the impact of glycemic control and the delay in lung maturation. We now have the technology to synchronize planned deliveries and lung maturity. The contemporary approach to fetal surveillance testing and the recognition of the importance of glucose control enables us to minimize planned deliveries for fear of fetal demise. On the other hand, perhaps this is an opportune time to consider planned delivery for the oversized fetus (macrosomic) in order to prevent shoulder dystocia and its accompanying complications.[22] This study compared patients delivered between 36 0/7–38 6/7 weeks to a group who delivered between 39/40 weeks' gestation. Composite outcome, RDS, treated hyperbilirubinemia, and hypoglycemia were elevated in the early delivery group. In the study, even though lung maturity was found in the early delivery group, other problems existed such as hyperbilirubinemia and hypoglycemia that are more common in premature infants. Although the authors recommended postponement of delivery until 39 weeks, this endorsement was based on nondiabetic patients. The clinician needs to weigh the diabetic risk to the fetus against all other above described risks.

In our institution, we used the following approach for lung maturity testing before delivery. In patients with imminent fetal compromise or death as reflected by specific abnormal patterns of surveillance testing[23,24] or severe maternal complications that require immediate delivery/termination of pregnancy, delivery occurred without fetal lung testing. The rationale for this approach is that it is better to deliver a live baby with immature lungs than a stillbirth with mature lungs. In cases in which the indication did not pose an immediate risk to mother and fetus, for example, previous cesarean section or growth restriction but normal fetal surveillance testing results, only in the presence of positive lung maturity testing did delivery occur. If test results are negative, patients should be under strict surveillance and lung maturity testing needs to be repeated within a week.

Glycemic control should always be considered in the decision process to perform/not to perform lung maturity testing. In cases of poor glycemic control, regardless of gestational age, amniocentesis for lung maturity testing should be performed. On the other hand, in the presence of good glycemic control and reassuring dates for patients after 37 weeks' gestation, delivery can be performed without prior testing. This approach will decrease the number of unnecessary invasive procedures performed to confirm or refute lung maturity.

FETAL OVERGROWTH OR UNDERGROWTH IN THE DIABETIC PREGNANCY

Being relatively common and easily documented, macrosomia or growth-restricted fetuses are the primary perinatal outcome most investigators refer to when addressing GDM. Growth diversity is related to relevant surrogate complications such as cesarean section, shoulder dystocia, and brachial plexus injury (BPI) and perinatal mortality.[25] Clinicians managing diabetic patients, especially with severe fetal growth restriction and Doppler changes need to decide whether to deliver immediately or to strive for a longer period for maturation to occur. Within the delayed group[23,24] more intrauterine deaths but fewer neonatal deaths occurred compared with the immediate delivery group. For infants who survived, the study showed that there was little difference in their cognition or motor scores or in their parents' assessment of their behavior; these findings were similar to those of the general population. However, these results still do not benefit the decision-making process for the physician managing a patient in these conditions.

Macrosomic fetuses are born to both diabetic and nondiabetic mothers. The rate of macrosomia in nondiabetic mothers is approximately 8%–9%; in diabetic mothers, the reported rate is 20%–50%. Do all macrosomic fetuses experience the same risks or does genetic predisposition toward greater birth weight or the intrauterine environment alter both long- and short-term consequences of macrosomia? Different definitions of weight persist to define the macrosomic fetus. The American College of Obstetricians and Gynecologists has defined macrosomia as birth weight or estimated fetal weight (EFW) greater than either 4000 or 4500 g, irrespective of gestational age. Therefore, the rate of reported macrosomia will be influenced by the weight threshold used in a study. Esakoff et al.[26] compared two groups of macrosomic neonates (weight ≥4000 g) from GDM and the other from non-GDM mothers. He found that the adjusted odds ratio (OR) was 2- to 10-folds higher for hyperbilirubinemia, hypoglycemia, and neonatal RDS; for shoulder dystocia 16.45(6.71–40.33) and BPI 41.89(4.05–433.64) for the diabetic macrosomic group in comparison to the reference group. We also evaluated 75,363 consecutive vaginally delivered infants from our departmental database (1970–1985). Gravids were stratified into diabetic and nondiabetic groups and further by weight category (> and <4000 g). The analysis revealed that the infants of the diabetic women were at higher risk compared to the nondiabetic group: (1) a fourfold risk for macrosomia; (2) overall, the risk for shoulder dystocia was 5.9 (95% CI: 4.4–8.0) for diabetic women; (3) shoulder dystocia for diabetic patients in both weight categories: <4000 g (RR 2.60; 95% CI: 1.3–5.3) and ≥4000 g (RR 3.4; 95% CI: 2.4–4.8). See Table 37-2.

Other major factors that influence practitioner decision making on timing of delivery are the likelihood of shoulder dystocia and the potential for permanent brachial plexus nerve palsy. Shoulder dystocia is rare with an incidence of 1–5/1000. Therefore, the average obstetrician has limited skill in addressing this complication. But, shoulder dystocia has been aptly described as "the infrequent, unanticipated, unpredictable nightmare of the obstetrician."[27] This condition is associated with high rates of morbidity and mortality and increased numbers of medical liability cases out of any proportion to the rate of its occurrence. Most lawsuits involving shoulder dystocia allege negligence as the cause of BPI, fracture of clavicle and humerus, fetal death, brain damage, and other neonatal and maternal injuries. In a review addressing the medicolegal risks of shoulder dystocia, Zylstra et al.[28] retrospectively reviewed all cases over a seven-year period closed by the Boston-based ProMutual Group, a major liability insurance carrier. The most characteristic prenatal factor associated with litigation was gestational diabetes and obesity involving 38/61 cases closed with an indemnity payment. The total indemnity was $20,745,000.00 with a mean indemnity of approximately $546,000.00. The intrapartum factors associated with litigation of shoulder dystocia cases included prolonged second stage, oxytocin induction and augmentation, forceps delivery, and vacuum extraction involving 43/61 cases. These cases closed with a total indemnity payout of $25,954,100.00. The mean indemnity was approximately $603,600.00. These examples demonstrate the magnitude of the problem and the economic costs surrounding this issue. The reader should note that this data come from a single information source, in a single city, from a single state. When you

TABLE 37-2 Compression of Perinatal Complications by Neonatal Size

	Nondiabetic <4000 g	Nondiabetic ≥4000 g	Diabetic <4000 g	Diabetic ≥4000 g	Total Cases
No complications	61.6%	55.2%	59.3%	54.7%	61.0%
Preeclampsia	6.6%	6.8%	12.7%	18.0%	6.8%
Trauma	0.5%	1.5%	1.1%	3.7%	0.6%
Fetal distress	17.8%	24.1%	18.1%	33.3%	18.3%
Delivery complications	23.5%	31.3%	20.8%	44.0%	24.1%
Birth defects	2.4%	2.9%	4.2%	6.7%	2.5%
Shoulder dystocia	0.2%	4.2%	0.6%	19.0%	0.6%
Stillbirth	1.2%	1.2%	4.2%	12.2%	1.2%
Total cases	68.115	5.668	1253	327	75.363

consider the numerous databases, collecting data from thousands of cities in all 50 states, the documented injuries and their economic ramifications are staggering.

Adverse neonatal outcome involves a substantial number of neonates. We reported that in nondiabetic neonates with shoulder dystocia, 37% had one or more complications (Figure 37-1).[27] The rate increased to 81% in infants of diabetic mothers (Figure 37-2). BPI occurred in about 15% (range 4%–40%) of the shoulder cases, 20% of these being permanent injuries. Therefore, overall, there are about 3% (range 3%–10%) of cases with permanent injury.[29–32]

There is a significant proportion (34%–47%) of BPIs that are not related to shoulder dystocia; 4% of injuries occur after cesarean section delivery.[33–37] BPI can occur without the involvement of any traction or physical force. It was reported to be associated with precipitate vaginal delivery.[29] In addition, in some cases, the BPI occurs in the posterior arm and not in the anterior arm that was impacted against the symphysis pubis.[29,32,33,38–40] Hypoxic-ischemic encephalopathy and even death may also be the end result of shoulder dystocia.[36,40] In addition, asphyxia is more common and occurs during labor even in cases when diabetes is not present.[36] Finally, some authors suggest that infection such as toxoplasmosis, coxsackievirus, mumps, pertussis, or mycoplasma pneumonia may be a cause for BPI.[29] Performing serial electromyelograms within the first seven days of life to establish a prenatal rather than intrapartum etiology has been suggested. A positive electromyelogram within one week of birth would suggest antepartum causation.[29,41] Just as the rate of shoulder dystocia goes up with increasing birth weight, so too does the risk of injury when shoulder dystocia occurs. Ecker et al.[42] found a RR for BPI of 9.6 for infants weighing >4000 g versus <4000 g; the RR increased to 17.9 and 45.2 at birth weight thresholds >4500 and 5000 g, respectively. Increasing birth weight, maternal diabetes, and vaginal delivery were all independently associated with an increased risk for BPI. Some authors use the definition of macrosomia based on the weight cutoff of 4500 g because the risk for BPI increases from 18% (>4500 g) to 45% (>5000 g) compared to baseline. However, there is a tenfold increase in BPI in the 4000 g weight threshold. As the majority of diabetic fetuses are below the 4500-g weight category, not addressing the problem of BPI in this group will result in a high number of infants exposed to the injury (Figure 37-3 and Table 37-3).

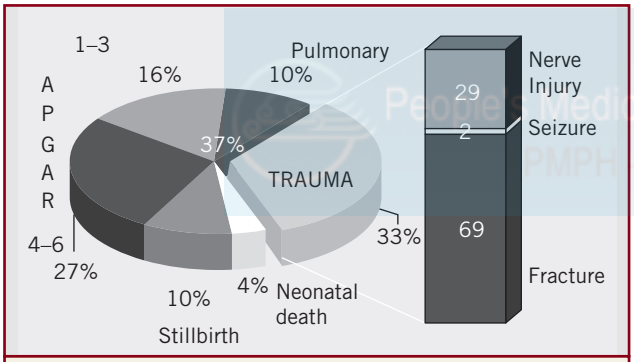

Figure 37.1 Nondiabetic 37% complication rate (one or more).

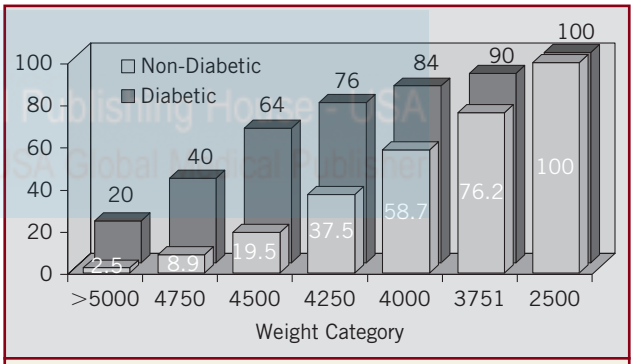

Figure 37.3 Cumulative incidence of shoulder dystocia by weight categories.

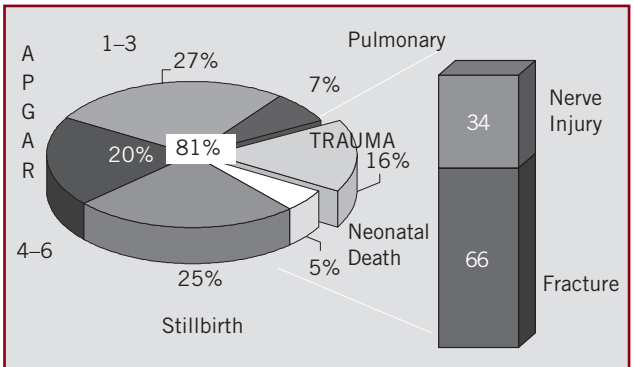

Figure 37.2 Diabetic mother 81% complication rate of shoulder dystocia (one or more).

TABLE 37-3 Rate (%) of SHD by Weight Categories

Weight	Diabetic	Nondiabetic
2500–3750	0.5	0.2
3751–3999	1.2	1.0
4000–4249	3.0	2.6
4250–4499	6.9	5.0
4500–4749	21.8	7.5
4750–4999	35.7	12.9
≥5000	38.5	8.9

The overgrown fetus of a diabetic mother is at an increased risk for serious adverse outcomes because of shoulder dystocia during vaginal delivery. Traditionally, authors have emphasized Erb's palsy as the single most significant complication when shoulder dystocia occurs. However, the prevalence of Erb's palsy is relatively low. Shoulder dystocia without Erb's palsy remains a serious complication involving bone fractures, asphyxia, and even fetal death. Cesarean delivery greatly reduces the likelihood of such outcomes and may, therefore, be used as the primary prevention approach. However, it should be noted that cesarean delivery does not eliminate the possibility of fetal and/or maternal complications (increased maternal blood loss, traumatic organ injury [ureters], infection, as well as other long-term complications). Therefore, although cesarean section rates are increasing universally, the benefit–risk ratio should be assessed for any given complication before surgery.

CAN SHOULDER DYSTOCIA BE PREDICTED?

We cannot predict shoulder dystocia with a high level of accuracy. However, we can identify risk factors that contribute to this complication. Our mission is to attempt to prevent shoulder dystocia or at minimum to significantly decrease this condition. The name of the game is prevention, not prediction. Several prenatal risk factors for the development of shoulder dystocia have been suggested. They include diabetes, maternal obesity, excessive weight gain, postdate pregnancy, previous shoulder dystocia,[43–45] fetal macrosomia, and multiparty.[27,30–35,46–53] Although all these factors have been suggested in univariant design studies as contributors for the risk of the complication, they are all associated with fetal macrosomia and, therefore, the question remains if it is the macrosomia, obesity, or a combination of both that is responsible for the occurrence of shoulder dystocia in labor.

The major dilemma for the obstetrician is the poor predictive power of methods for fetal weight assessment and particularly shoulder width in the fetus. Coupled with this is the dynamic interaction between the maternal pelvic girdle, the power of the uterine contractions, maternal expulsive efforts, and the fetal diameters that will ultimately determine whether the shoulders pass easily through the outlet of the maternal pelvis. Fetal weight alone is a poor predictor. Two parameters should be addressed when evaluating the relationship between shoulder dystocia and birth weight. First, is the complication more common in a given weight threshold? In cases with shoulder dystocia, approximately 40%–50% will occur within the infant group weighing <4000 g.[27,53] The second question is which weight group will account for the largest number of shoulder dystocia cases. The number of gravid women whose fetuses weigh <4000 g are the majority, while the total number of infants weighing >4000 g is about 8%–10%. Therefore, despite the even distribution of shoulder cases, the total number of cases will be greater in the lower weight group.[54–56]

In diabetic patients, the majority of shoulder dystocia cases occur among macrosomic infants born vaginally. In a cohort study of nearly 75,000 nondiabetic women, the rate of macrosomic infants was 7.6% compared to 20.6% in the 1500 diabetic women. Nondiabetic women had an overall shoulder dystocia rate of 0.5% compared to 3.2% in diabetic women. The shoulder dystocia rate was 0.3% when birth weight was <4000 g in diabetic patients. Macrosomic infants of diabetic mothers had a more than threefold higher risk of shoulder dystocia than macrosomic infants of nondiabetic pregnancies (14.7% vs. 4.4%). In this study, we sought to evaluate if cesarean section delivery in a given weight category had an impact on the rate of shoulder dystocia if all patients were delivered by cesarean section at this weight threshold. We[27] performed a retrospective analysis stratifying all neonates by actual birth weight within each 250-g birth weight category. The cumulative rate of shoulder dystocia in the categories >4000 g was 84% for the diabetic and 58% for the nondiabetic women. The incidence of macrosomia varies depending on glycemic control in a given population assuming rates of 8%–30% (80–300/1000). In contrast, in the nondiabetic population, which is the majority of pregnant women, using our study population, approximately 7,200 out of 75,000 live births would have to be delivered by cesarean section. In this theoretical model, we found that for diabetic patients, the rate of cesarean section would increase by 0.43% if the threshold was 4000 or greater preventing 84% of the shoulder cases. If the threshold is 4250 g, 76% of shoulder cases would be prevented. Using a higher threshold of 4500 g recommended by American College of Obstetricians and Gynecologists (ACOG)[57] will increase the cesarean section rate by 0.14% but will still leave 46% unidentified shoulder cases. Therefore, the ACOG-recommended threshold does not address the main problem of how to decrease and prevent shoulder dystocia in diabetic patients. For nondiabetic patients, as approximately 50% of shoulder cases occur below 4000 g, any threshold above 4000 g that requires cesarean delivery will result in fewer cases of shoulder dystocia. To obtain the same effect of decreasing shoulder dystocia as in diabetic patients, a lower threshold of 3750 g would need to be used for the nondiabetic patients. Using this threshold increases the cesarean section rate by 17% but identifies 76% of shoulder cases. However, in nondiabetic women, using this approach will place the mother at greater risk with operative delivery than the benefit to the fetus in avoiding shoulder dystocia (Figure 37-3 and Table 37-4).

In summary, ACOG recommends that cesarean section be considered when EFW exceeds 5000 g. However, it should be noted that only 1.5% of shoulder cases weigh more than 5000 g. Moreover, 13.2% of shoulder cases will be in the 4500–4999 g weight category whereas 85.3% will be between 4000–4999 g. Therefore, these recommendations will not, in all practically, result in a change in the overall rate of shoulder dystocia in the population. ACOG also recommends that in diabetic patients cesarean section should be considered when fetal weight is ≥4500 g. Again, the majority of shoulder cases will be missed (Figure 37-3 and Table 37-4).

In contrast to ACOG recommendations, our policy is that recognition of risk factors (obesity, previous shoulder dystocia, etc.) for shoulder dystocia before delivery be incorporated into clinical decision making. In nondiabetic patients, trial of labor for all fetuses with weight >4000 g should be attempted with liberal policy toward cesarean section in the presence of labor abnormalities.[27] A cesarean delivery is recommended for diabetic patients with weight estimation 4000–4250 g. The specific threshold should be determined based on level of glycemic control achieved in a given institution and the accuracy of the ultrasonography

TABLE 37-4 The Net Cumulative Contribution to Overall Cesarean Section by Weight Categories

	DM		Non-DM	
Weight	% C/S	% SHD	% C/S	% SHD
3750	0.76	90	16.8	76.0
4000	0.43	84	7.5	58.7
4250	0.26	76	3.1	37.5
4500	0.14	64	1.2	19.5
4750	0.07	40	0.4	8.9
>5000	0.03	20	0.1	2.5

C/S, Cesarean section.

measurement. Using higher thresholds (4500 g) will not result in significantly decreasing rates of shoulder dystocia.[27]

WHY IS SHOULDER DYSTOCIA MORE COMMON IN INFANTS OF DIABETIC MOTHERS?

The anthropometric differences explain the discrepancy in the risk for shoulder dystocia between diabetic and nondiabetic women. In nondiabetic women, macrosomia is constitutional in origin, resulting in a proportionally larger infant. In contrast, for the diabetic macrosomic infant, its overgrowth is due to continuous fetal hyperinsulinemia resulting in disproportional growth and organomegaly in the majority of organs with the exception of the brain. There is a significant difference in several anthropometric measures such as abdominal and shoulder circumference as well as an increase in fetal fat mass distribution. Organ overgrowth is used as the marker to identify the fetus compromised by diabetic macrosomia.[54,56,57] When comparing the macrosomic fetus of a diabetic to a nondiabetic mother, the infant is disproportionately larger, with much of the excess weight distributed in the trunk and shoulders. This increased chest-head and shoulder-head size discrepancy results in a higher risk for shoulder dystocia (Table 37-5).[42,57,58]

TABLE 37-5 The Relative Risk for Shoulder Dystocia by Birth Percentile

DM vs. Non-DM	RR	95% CI
50	n.s	n.s
75	7.4	2.7–15.2
90	4.9	2.4–10.4
95	8.8	4.6–16.9
97	13.9	6.1–31.8
99	6.8	3.4–13.5

FETAL BODY COMPOSITION AND WEIGHT DISTRIBUTION

The body composition and weight distribution of infants of diabetic women differ from those of nondiabetic women. The fat mass accounts for a substantial portion of the variance in the birth weight between the two babies.[59] Calculating a ratio between weight and length to determine if a baby is LGA may not be an accurate reflection of the differences in weight distribution. A study of LGA neonates (diabetic vs. nondiabetic mothers) reported no differences in birth weights, lengths, and body mass indices between both groups. However, the infants of diabetic mothers had a significantly greater sum of skinfold thickness (a measure of subcutaneous fat) than that of infants of nondiabetic mothers.[60]

The average maternal glucose concentrations or other metabolic factors characteristic of diabetic women may have influenced the variance in weight distribution. Keller et al.[61] reported an asymmetrically large group of LGA neonates of type 1 diabetic mothers with abdominal circumference >90th percentile and biparietal diameters <90th percentile; symmetrically large babies had both measures >90th percentile. The HbA1c of the asymmetrical group was significantly greater than that of the symmetrical group. This may imply that the differential distribution of truncal fat in infants of diabetic mothers may be more dependent on maternal glucose concentrations than on overall constitutional fetal growth.

CESAREAN DELIVERY IN PREVENTING SHOULDER DYSTOCIA AND FETAL INJURY

Discounting vaginal delivery for the large fetus of a diabetic mother generally precludes the potential for shoulder dystocia. Consequently, the risk of nerve and bone injury, as well as the more serious outcomes of birth asphyxia and intrapartum death as a consequence of shoulder dystocia is also eliminated. Although it is recognized that BPI can occur in the setting of cesarean delivery, the risk associated with vaginal birth is much greater.[62–64] A population-based study of births in Washington State, USA, revealed no reported cases of brachial or Erb's palsy from over 13,000 consecutive cesarean deliveries.[59] Therefore, in the majority of cases,

performing a cesarean section will prevent Erb–Duchenne palsy and is the preferred method of delivery of the large fetus.

The practicality of elective cesarean section for prevention of shoulder dystocia is hampered by the difficulty to identify the macrocosmic fetus antenatally. Using the data from the above and other studies, Rouse et al.[35,65] used a decision analysis model and estimated that 2345 cesarean deliveries will be required at a cost of $4.9 million annually to prevent one permanent injury resulting from shoulder dystocia if all fetuses suspected of weight 4000 g or more underwent cesarean delivery. They recommend that EFW greater than 5000 g in women without diabetes and estimated weight >4500 g in diabetic women be a consideration for cesarean delivery. Unfortunately, these recommendations were included in the ACOG Technical Bulletin addressing shoulder dystocia.[51] Rouse et al.[35,65] and the ACOG[55] Technical Bulletin did not take into account that the incidence of macrosomia varies significantly depending on level of glycemic control. In programs whose participants achieved levels of glycemic control, the reported incidence of macrosomia was 3%–8%, which significantly reduced the need for elective delivery (cesarean delivery or induction). The authors quoted the costs in millions required to prevent one shoulder dystocia; however, they failed to include the cost of malpractice because of shoulder! These days, with the rise in cesarean section rates, recommendations for elective cesarean section for previous cesarean delivery and the argument advocating cesarean delivery by patient demand, the overall cesarean delivery rates will be minimally affected by the addition of cesarean delivery for fetal macrosomia of diabetic patients (0.26%–2.0% increase). The moral issue is not between what is right or wrong because we inherently understand and recognize the difference. What ultimately is being weighed is "what is 'more' right?" When all of us are working under the ethical mandate of first, do no harm (*primum non nocere*), the question if we can place a price on an infant or mother's life or on BPI remains unanswered moral dilemmas.

Rouse and Owen[65,66] calculated the probability of shoulder dystocia based on birth weight in diabetic and nondiabetic pregnancies. For birth weights ≥4500 g, there is a 52% probability in diabetic compared to 14% in nondiabetic pregnancies. The mean probability that a neonatal BPI will persist was 6.7% (range 0%–19%). They calculated that to prevent one case of permanent BPI in babies weighting ≥ 4500 g, it would necessitate performing 153 cesarean deliveries in diabetic and 419 in nondiabetic mothers. If a cutoff of 4000 g is used, then 169 cesarean sections would be required in diabetic versus 654 in nondiabetic women. Rouse and Owen[65,66] updated their initial analysis by factoring in information from population-based studies on the frequency of BPI, both transient and persistent. These calculations suggest that an even greater number of cesarean sections need to be performed to prevent permanent palsies. However, Erb's palsy should not be the only consideration in evaluation of morbidity prevention by cesarean delivery. Although Erb's palsy is a severe complication, bone fractures, asphyxia, respiratory complications requiring neonatal intensive care admission, and neonatal and fetal demise should be considered when calculating the cost of cesarean sections performed to prevent shoulder dystocia and adverse outcome. In fact, when the composite outcome approach is used, 81% of shoulder dystocia cases from infants of diabetic mothers will be identified compared to 34% for infants of nondiabetic mothers.

Mullin et al.[67] examined the results of their unit's policy of offering cesarean delivery to all diabetic women with EFW >4250 g (by sonographic or clinical means). Of 72 women meeting this fetal weight threshold during a three-year period, 61% opted for cesarean delivery. Seventeen of the remaining delivered vaginally (39% cesarean section rate in women who labored), and four of these deliveries were complicated by shoulder dystocia (24%). On the basis of previously reported rates of BPIs, the investigators calculated the number of cesarean sections needed to prevent one case of permanent Erb's palsy. In diabetic women, approximately 100–400 cesarean sections would result in avoidance of one case of permanent palsy. This number is somewhat more favorable toward a policy of prophylactic cesarean section than that estimated by Rouse. This highlights the fact that cost-benefit ratios of prophylactic cesarean sections for suspected macrosomia in diabetic women may be most meaningful when calculating for, and applied to, an individual population taking into account overall morbidity rather than a single outcome parameter. Different maternity units report varying cesarean section rates for diabetic patients from 15% to 80% or more. The number of cesarean deliveries needed to prevent shoulder dystocia and Erb's palsy will be determined by the background rate of cesarean section in a given institution. Moreover, different diabetic programs report different rates of macrosomia (poor glycemic control), which again affects the rate of shoulder dystocia. Diabetic women's ability to achieve targeted levels of glycemic control may prove to be a salient factor in decreasing the rate of this complication in pregnancy.

Theoretical models provide a foundation for clinical studies. However, there is scant information on the clinical impact of a policy of prophylactic cesarean section in reducing the frequency of shoulder dystocia events. If there is no significant decrease in shoulder dystocia rate, there cannot be an accompanying decrease in BPI and other adverse outcomes. We[68] in a prospective study addressed this issue. Diabetic women were delivered by cesarean section when EFW by ultrasound was >4250 g, a threshold chosen to reduce unnecessary intervention because of sonographic error. Labor inductions of LGA fetuses with birth weights <4250 g were also performed. Although only 11% of the diabetic population was delivered by cesarean section or were induced for macrosomia, the shoulder dystocia rate among diabetic women dropped significantly on implementation of this procedure compared to the previous three years (1.5% vs. 2.8% [OR 0.5, 95% CI: 0.3–1.0]). Among macrosomic infants, the shoulder dystocia rate dropped from 19% to 7% (OR 0.3, 95% CI: 0.1–1.0). The cesarean delivery rate among diabetics rose from 21.7% to 25.1%. The results of this study demonstrated the possibility of reducing the rate of shoulder dystocia in diabetic women using prophylactic cesarean delivery for the macrosomic fetus. In this study, we found that the clinical accuracy of EFW using ultrasound for identifying macrosomic and nonmacrosomic infants was 86%. In 5.3%, macrosomia was missed; this group was delivered vaginally with a resultant 19% shoulder dystocia. In 7% of the cases, nonmacrosomic infants were misdiagnosed as macrosomic and were delivered. The clinical cost of incorrect EFW by ultrasound (7%, 96/1377) was 22 cases that underwent induction of labor and 17 cases had elective cesarean section per our protocol for LGA/

macrosomia. Twenty-two cases underwent induction of labor for other indications (e.g., preeclampsia); 8 cases had elective repeat section; 27 cases entered spontaneous labor. The impact of this protocol for the delivery of diabetic patients on our general obstetric population was an increased cesarean section rate of 1% and induction of labor for macrosomia 0.4%.

Several formulas based on different sonographic measurements of fetal organs have been developed to estimate fetal weight with varying accuracy and precision. For all methods, the accuracy of the fetal weight estimation decreases with increasing birth weight. Local formulas improve the EFW calculation. The combined formula can further optimize the accuracy and precision. Application of specific formulas for the small and the large fetus had the most pronounced effect in improving fetal weight estimation.[69,70]

In nondiabetic women, ultrasound biometry for the detection of macrosomia has a sensitivity of 22%–44%, a specificity of 99%, a positive predictive value of 30%–44%, and a negative predictive value of 97%–99%. Clinical studies have found no significant differences in absolute percent error of birth weight between infants of women with/without diabetes. The sensitivity and specificity of sonographic estimates of fetal weight in predicting birth weight of ≥90th percentile in diabetic pregnancies ranges from 70% to 96%, and 77% to 100%, respectively; corresponding values for predicting a birth weight of ≥4000 g are 33%–69% and 77%–98%, respectively. Ultrasonic estimation of fetal weight needs to take into account whether or not the mother has diabetes. Otherwise, there is a significant underestimation of fetal weight of >10% using conventional weight prediction tables.[71] Diabetic pregnancies, because of the larger fetal weight, are five times more likely to be complicated by shoulder dystocia than nondiabetic pregnancies (5% vs. 1.1% for birth weights ≥4000 g).[72]

BPIs are four times more likely in diabetic pregnancies. However, because of scant long-term follow-up, the prevalence of the permanency of the injury has not been well established.[65–66,73] Cesarean section rates for women with diabetes are significantly greater than for their nondiabetic counterparts in most series. Remsberg et al.[73] conducted a detailed analysis of 42,071 singleton births in South Carolina, USA. Diabetic mothers compromised 3.6% of the series, 80% of which had GDM. Of the preexisting diabetic patients, 51.3% underwent cesarean delivery, as did 34.4% of those with GDM. For nondiabetic women, 22.9% of births were by cesarean section. Regression analysis demonstrated an association between diabetes and cesarean delivery that was not a result of infant size alone. The strongest reported associations were related to disproportion, previous cesarean delivery, failed induction, and malpresentation. These results and those from other studies suggest that the physician practice patterns and not macrosomia are the contributors to the high cesarean section rates.[74-76]

One major factor that contributes to cesarean section rates is the presence of a cesarean section scar. Two studies examined perinatal outcome of vaginal birth after cesarean delivery (VBAC) in women with diabetes. In the Coleman study,[77] VBAC was offered if the sonographic EFA was <4000 g. Overall, the successful VBAC rate was lower in women with diabetes (64.1 vs. 73.2% [OR 1.90, 95% CI: 1.20–2.99]). This was not due to the higher induction rate in women with diabetes (OR 2.16, CI: 1.37–3.40). Women with diabetes who delivered vaginally were more likely to have an operative delivery: forceps (OR 2.71, CI: 1.15–6.45); vacuum (OR 2.59, CI: 0.89–7.73). Most importantly, there were no significant differences between the two groups in the incidence of shoulder dystocia, preeclampsia, pelvic lacerations, or prolonged hospitalization, and the only two ruptured uteri occurred in the control group. Blackwell et al.[78] compared diabetic women with/without a previous cesarean section delivery. In the previous cesarean section group, the rate of repeat cesarean section doubled (56.3% vs. 26.3%) with a successful VBAC rate of 43.7%. We can deduce from these studies that in women with diabetes who have had a previous cesarean delivery it is reasonable and safe to offer both a VBAC and induction of labor.

RATIONALE FOR ELECTIVE INDUCTION OF LABOR IN DIABETES

The foundation for the decision for an elective induction of labor is based on the risk of fetal demise with continuation of pregnancy, the accelerated in utero fetal growth, and the association between fetal macrosomia, shoulder dystocia, and fetal injury. Attempted delivery at term will result in lower cesarean section rates than when pregnancy progresses and fetal weight estimation is >4000–4250 g. Thus, even with a higher rate of cesarean section in the induced group, it will still be less than the expected rate if all patients were sectioned electively. However, insufficient data are available to justify recommending either for or against induction of labor at term in pregnancies complicated by diabetes. Thus, the practitioner who elects to induce labor for his/her patient is well advised to observe the usual precautions taken by attendant on inductions for all pregnancies: taking special care to follow maternal glucose and Pitocin administration during labor; have the appropriate personnel and equipment available for the management of possible shoulder dystocia.

Confounding Factors

There is paucity of information on the risks and benefits of induction of labor for pregnancies compromised by diabetes. Any plan of management for the induction of labor of a pregnant diabetic woman will need to resolve the confounding issues of cervical ripeness, labor management, epidural anesthesia, fetal body composition, and weight distribution and estimates of fetal weight. A large matched cohort study[79] compared the outcomes of labor between induced and spontaneous labor. Patients were matched for nulliparity, cephalic presentation, term gestation age, and actual birth weight between 3800 g and 4000 g. In the induced group, there was a higher incidence of cesarean delivery (for dystocia and nonreassuring fetal heart rate tracings) and increased instrumental deliveries. Bishop score was not part of the matching criteria. Because of the retrospective study design, it is possible that the spontaneous labor group had a higher Bishop score and therefore less cesarean and instrumental deliveries. In our study,[80] comparing induction of labor with spontaneous labor, the influence of cervical status at the onset of induction was addressed. Women with a Bishop score[81] ≤7 received vaginal prostaglandin as a cervical ripening agent. Regardless of the initial Bishop score, women undergoing labor induction and ripening of the cervix had a higher cesarean section rate than those with spontaneous delivery.

In another study,[82] subjects and controls whose initial Bishop score was ≤4 received either cervical misoprostol or placebo twice during the week following enrollment. There were no statistically significant differences between the misoprostol or placebo groups with regard to the Bishop score. The rate of spontaneous labor and difference in cesarean rates were not statistically significant. The objective of Nicholson's study[83] was to determine whether exposure of nulliparous women to a high rate of preventive labor induction was associated with improvement in birth health. A risk-scoring system was used to guide the frequent use of preventive labor induction in 100 nulliparous women. The birth outcomes of this group were compared with those of 352 nulliparous women who received usual care. Cesarean delivery was the primary study outcome. The Adverse Outcome Index and the rate of uncomplicated vaginal delivery were used to measure overall birth health. The exposed group experienced a higher labor induction rate (48% vs. 23.6%; $P = .001$), a lower cesarean rate (9% vs. 25.8%; adjusted OR, 0.36; $P = .02$), and better composite birth outcomes. They concluded that exposure of nulliparous women to a high preventive induction rate was significantly associated with improvement in birth health.

Although several studies have examined induction of labor for the indication of estimated macrosomia in nondiabetic women,[84–87] there have been few studies conducted solely on pregnancy complicated by diabetes.[88] The apprehension that higher morbidity rates are the result of delaying delivery until full-term prompted Kjos et al.[88] to conduct a randomized controlled trial of 200 pregnancies complicated by GDM. Patients were assigned either to elective delivery at 38 weeks or to expectant management, which included twice weekly cardiotocography and amniotic fluid volume evaluation. In a Cochrane Review[89] of this trial, they concluded that the risk of having a cesarean section was similar for both groups (RR 0.81, 95% CI: 0.52–1.26). The risk of macrosomia was reduced in the elective delivery group (RR 0.56, 95% CI: 0.32–0.98) and there were three cases of mild shoulder dystocia in the expectant management group. Because of the paucity of studies, they determined that either elective delivery at 38 weeks or expectant management is comparable.

In another study,[90] insulin-requiring well-controlled type 2 and gestational diabetic women were randomized to either induction of labor or expectant management at 38 weeks. The mean gestational age difference between groups at delivery was 1 week and the mean difference in birth weight was 226 g. With the assumption that diabetic infants gain 40–60 g daily (50 g × 7 days = 350 g), no difference was found between the 2 groups. Thus, gestational age cannot provide the explanation to the three shoulder cases in the expectant management group. In addition, the small sample size exposes this study to both α and β errors.

CAN LABOR ABNORMALITIES PREDICT SHOULDER DYSTOCIA?

Several authors[43–45,91–93] sought to evaluate delivery mode management decisions and the rate of shoulder dystocia recurrence for women with a prior delivery complicated by shoulder dystocia. One study[91] included all vaginal deliveries complicated by shoulder dystocia from 1996 to 2001. In the initial five-year period, 205 shoulder dystocia cases (0.8%) and 36 (17.5%) neonatal injuries were identified. In the shoulder dystocia cases, 39 patients had 48 subsequent deliveries. In the trial of labor cases that resulted in vaginal deliveries, the rate of recurrence of shoulder dystocia was high—approximately 10 times higher than the rate for the general population. There is scant information reporting the association between labor abnormalities, induction of labor, and shoulder dystocia. Acker et al.[53] compared the rate of shoulder dystocia in women who delivered infants weighing 3500–4000 g either in spontaneous labor or low forceps. The low forceps group had two- to threefold higher rates of shoulder dystocia in normal and abnormal labor including prolonged latent phase, protraction disorder and arrest disorder. Gross et al.[31] evaluated the association between shoulder dystocia and dysfunctional labor in infants weighing >4000 g. The rate of shoulder dystocia was approximately twofold higher in the rate category >4500 g in comparison to infants weighing 4000–4499 g. However, even in the lower weight category, the rate of shoulder dystocia was 15%–38% depending on the labor abnormality. In another study, a significant association was found between active-phase abnormalities and shoulder dystocia but it included only 36 patients.[94] In a retrospective analysis of 52 cases of shoulder dystocia, the authors reported no differences in labor abnormalities.[95] A large study comparing 276 consecutive cases of shoulder dystocia with 600 matched controls did not identify labor patterns as predictive among any cohort even those with diabetes or macrosomia. The study found significantly higher rates of shoulder dystocia in induction of labor. This may in part be due to fetal size that itself is associated with shoulder dystocia.[96] Although there is scant data addressing labor abnormalities and shoulder dystocia, it is recommended that the care provider be diligent to the occurrence of labor abnormalities and patients during induction of labor especially diabetic and/or obese women. However, the labor curve is not an absolute predictor of shoulder dystocia. Therefore, labor augmentation with careful monitoring the Pitocin administration should be the approach of choice in the presence of fetal macrosomia rather than routine cesarean delivery.

SHOULDER DYSTOCIA IN LABOR: BETWEEN A ROCK AND A HARD PLACE?!?

Shoulder dystocia is unpredictable by statistical analysis. However, several conditions, such as maternal obesity, previous and current macrosomia, previous shoulder dystocia, labor abnormality, induction of labor, and instrumental delivery are likely suspects for an impending shoulder dystocia that should set off "anticipatory alarms" for the obstetrician. "Forewarned is forearmed"—those who know something is coming are better prepared to face it than those who do not know. In our study[68] when practitioners were "asleep on the watch," in cases not identified as macrosomic by ultrasound exam, the rate of shoulder dystocia was 19%. Although shoulder dystocia is rare, and not all cases of brachial plexus can and/or should be attributed to obstetrician mismanagement, a plaintiff's lawyer will fault for failure to estimate fetal weight, perform timely cesarean delivery, use appropriate maneuvers correctly, use of inappropriate or excessive lateral traction of fetal head, or have a pediatrician present.[28,29,98] When shoulder dystocia occurs, the goal is to free the impacted shoulder as quickly as possible as the fetus can tolerate only 8–10 minutes

before development of permanent neurological damage. Gherman et al.[99] demonstrated that the head to shoulder interval to delivery at >7 minutes has sensitivity of 67% and specificity of 74% for predicting brain injury in a case controlled study.

Multiple maneuvers have been suggested for the release of shoulder dystocia. The obstetrician needs to master the most common maneuvers so that under duress, the maneuver becomes automatic, efficient, and hopefully effective. The maneuvers most commonly applied are the McRoberts', suprapubic pressure, the Wood's corkscrew and extraction of the posterior arm. In our study, we found that 45% of the shoulder cases can be released with one maneuver, 39% with two, and 11% with three. The need for four maneuvers was 4% and five maneuvers for 1% of cases.[97] Furthermore, the incidence of Erb's palsy and fractures range from 6% to 10% when one or two maneuvers were used and increased to over 20% when three or more maneuvers were applied. Because of its simplicity, it is reasonable to recommend performing the McRoberts' maneuver as the initial maneuver, which requires hyperflexion and abduction of the hips causing rotation of the symphysis pubis and flattening of the lumbar lordosis that frees the impacted shoulder.[100,101] Suprapubic pressure may be applied at the same time to support dislodging the impacted shoulder.[102] The pressure should be directed backward and downward; anterior pressure will impact the shoulder even further. Performing an episiotomy has been debated. It is the author's opinion that a wide episiotomy should be performed in these cases if additional maneuvers are needed to create more space for the manipulations. Performing an episiotomy alone, however, will not release the impacted shoulder. Finally, when the conventional maneuvers fail to release the shoulder, the Zavanelli maneuver (cephalic replacement) is a potential option.[103,104] Manipulations that include fundal pressure, frantic tugging and pulling of the head, exerting excessive strength instead of applying guarded and directed strength, and rotation of the head rather than rotation of the shoulders must never be included in the maneuver options. The approach to management of shoulder dystocia was aptly described by Hopwood's poem.[105]

If shoulder dystocia brings you grief,
Oblique diameter spells relief.
Extending episiotomy will be your boon
To gain posterior vaginal room.
If corkscrewing still leaves you colder,
Then gently deliver the posterior shoulder.

SUMMARY

With the currently available data, it is difficult to provide the clinician, with any degree of certainty, what the threshold should be for performing an elective cesarean delivery in women with diabetes. Shoulder dystocia in a previous delivery will influence the decision on mode of delivery unless the EFW is significantly less than that of the previous birth weight. Unless obstetric complications dictate otherwise, the uncomplicated (normal estimated birth weight, amniotic fluid volume, and metabolic control) diabetic pregnancy, both pregestational and gestational, can be allowed to go into spontaneous delivery at full term. Induction of labor and planned VBAC carry no greater risks than for a nondiabetic pregnancy. This will result with a relatively large number of patients who can undergo spontaneous vaginal delivery rather than being electively induced with the accompanying risk for this procedure. Elective cesarean section for the pregnant diabetic patient should be actively considered if the EFW is ≥4000–4250 g (Figure 37-4).

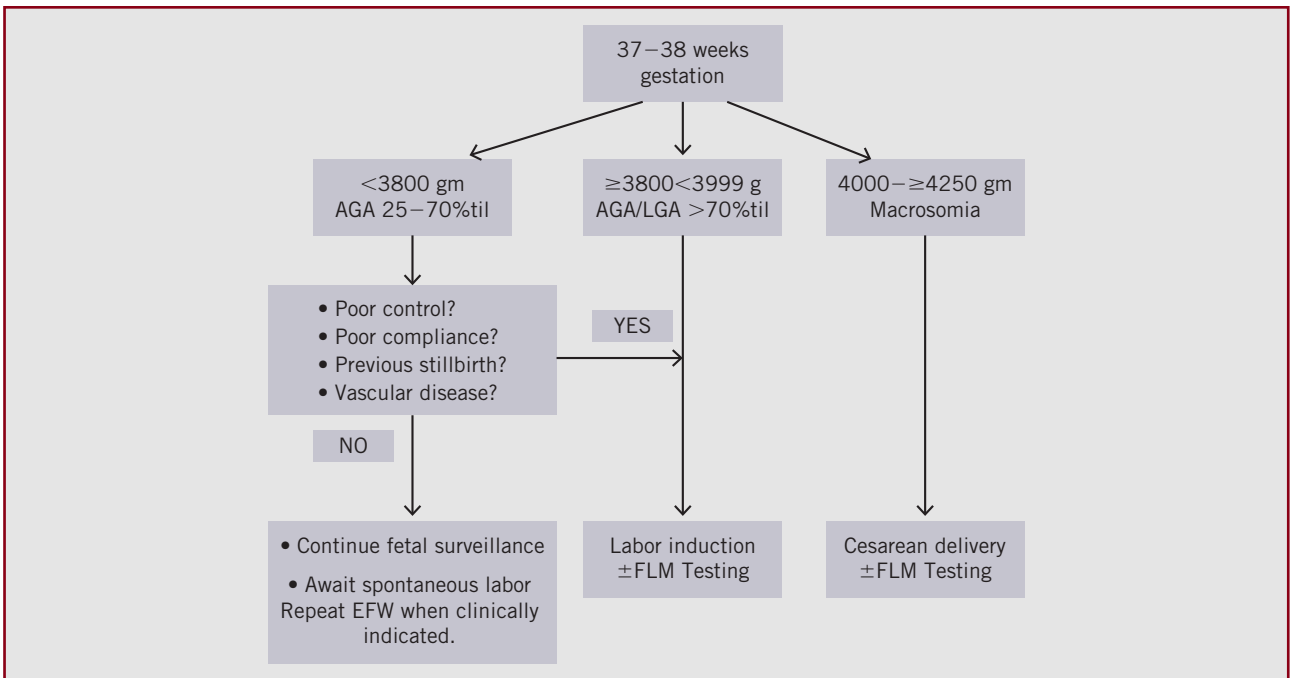

Figure 37.4 Timing and mode of delivery.

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Management of Labor: Augmentation, Induction, and Glucose Control

38

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The right thing at the wrong time is the wrong thing

—Joshua Harris

Key Points

- The risk of stillbirth, large-for-gestational age fetus, macrosomia, and shoulder dystocia remain major factors in labor induction.
- The condition of the cervix (score ≥4) will be a major factor in determining induction success rate.
- Both low- and high-dose oxytocin can be used for augmentation of labor; however, the high-dose regimen will result in shorter delivery time and fewer complications.
- The main goal during labor is to maintain the glycemic profile between 70 and 90 mg/dL; there are several strategies for insulin administration to achieve this goal.

INTRODUCTION

Why, when, and how to deliver the pregnant diabetic patient are fundamental questions in the management of diabetes in pregnancy. The scope of this chapter is to attempt to describe the "How." The mode of delivery, vaginal versus cesarean, of the diabetic patient remains controversial. Both induction of labor and cesarean delivery are common interventions in women with pregnancy compromised by diabetes. The rates of cesarean delivery in diabetic women are high; anywhere from 45% to 81%.[1,2] Failed labor inductions and elective cesarean delivery contribute to these rates. The underlying reason for intervention (labor induction or cesarean delivery) is the increased rate of both perinatal morbidity and mortality associated with the infants of diabetic mothers. Reasons for elective delivery include prevention of stillbirth, fetal overgrowth, macrosomia, and shoulder dystocia. Also, a significant number of diabetic patients will go into labor spontaneously whereas some will require augmentation of labor. Data pertaining exclusively to labor in diabetic patients is limited; the actual methodologies of labor augmentation and induction are no different than in other obstetrical encounters.

LABOR AUGMENTATION

Most women with gestational and preexisting diabetes who achieved targeted levels of glycemic control and are free of obstetric/medical complications are allowed to go into spontaneous labor. Some of them will develop labor dystocia and will require augmentation of labor. Labor abnormalities in diabetic patients are a concern, and most clinicians maintain a low threshold in diagnosing and responding to them. The main concern is the occurrence of shoulder dystocia during labor. However, the association between labor abnormalities, Pitocin, and augmentation remain unsettled. McFarland et al.[3] in a large study did not identify any labor patterns predictive of shoulder dystocia, even in those pregnancies complicated by diabetes and macrosomia. Lurie et al.[4] in a retrospective analysis of 52 cases of shoulder dystocia reported no difference in labor abnormalities and mean duration of second stage of labor. Gemer et al.[5] reported a significant association between labor abnormalities and shoulder dystocia.

Abnormal progression of labor can result from abnormalities of power, that is, inadequate uterine contractions, passenger (size, position, presentation), or passage (soft tissue and pelvis). Augmentation of labor should be considered when the patient is diagnosed with a protraction or arrest disorder, secondary to inadequate power, that is, less than three contractions in 10 minutes, or the intensity of the contractions is less than 25 mmHg. above baseline, or both. In all cases, the clinician must be watchful for labor abnormalities in large-for-gestational age and macrosomic fetuses, as these remain a major concern when augmenting diabetic patients.

The obstetrician's knowledge that the patient has diabetes has been shown to lower the threshold for performing a cesarean

delivery.[6] Assessment and documentation of the pelvis, fetus, and uterine contractility is imperative before initiating augmentation of labor. Oxytocin administration is appropriate only after such an assessment. The goal of oxytocin administration is to achieve cervical change and descent of the presenting part while avoiding uterine hyperstimulation and fetal compromise.

To make a diagnosis of arrest disorder in the first stage of labor, the following criteria should be used: the latent phase is completed and uterine contractility is equal or exceeds 200 Montevideo units.[7] Several oxytocin regimens are appropriate for labor stimulation; these regimens fall mainly in two categories: low- and high-dose oxytocin.[8–12] One of the leading investigators of insulin requirements during augmentation of labor was Joseph Seitchik of the University of Texas at San Antonio.[9] He recommended that when oxytocin is needed, the starting dose should be 0.5–1 mU/min or 1–2 mU/min every 30–40 minutes or every 15 minutes, respectively. This was coined the low-dose oxytocin approach. Maximum recommended doses in these regimens are 20 mU/min and 40 mU/min, respectively.

We and others[8,10,11] evaluated the effect of using high-dose oxytocin in the presence of labor abnormalities. In high-dose regimens, 4 or 6 mU/min are used as a starting dose and the incremental increase is the same, 4 or 6 mU/min, every 15–40 minutes up to a maximum dose of 40–42 mU/min. In our study[10] using a randomized block design, we found that the rate of cesarean delivery in the low-dose oxytocin group was 25.6% compared to the 10.4% in the high-dose group (relative risk [RR] 2.47, 95% confidence interval [CI]: 1.44–4.22). For nulliparous women, the low-dose oxytocin group had a 27.7% cesarean section rate compared to 11.1% receiving high-dose oxytocin (RR 2.49, 95% CI: 20–5.17). For multiparous women, the low-dose oxytocin group had 22.6% rate of cesarean delivery compared to 9.8% for the high-dose oxytocin group (RR 2.31, 95% CI: 04–5.17). Our study suggests a significant benefit in the rate of cesarean delivery with the high-dose regimen. An additional benefit of this approach includes shorter delivery time, fewer cesarean deliveries, and a reduced amount of intrapartum chorioamnionitis and neonatal sepsis.[7,8,10,11]

An additional question is when to start Pitocin augmentation or how long the obstetrician should wait before declaring a labor abnormality that requires intervention. Although the classic definition[7] of arrest disorder in the first stage of labor remains two hours without cervical change with a uterine contraction pattern of ≥200 Montevideo units, there are reports suggesting the use of a four-hour limit.[13] Before the implementation of such a rule, larger studies documenting efficacy and safety are needed. Also, this study did not specifically address pregnant diabetic patients; therefore, caution should be exercised when extrapolating its results.

LABOR INDUCTION

Induction of labor is on the rise in the United States, increasing from 9.5% in 1990 to 22.1% in 2004. Although it is not clear what proportion of these inductions are elective (i.e., without a medical indication), the overall rate of induction of labor is rising faster than the rate of pregnancy complications that would lead to a medically indicated induction. However, the maternal and neonatal effects of induction of labor are unclear. Many studies compare women with induction of labor to those in spontaneous labor. This is problematic because at any point in the management of the woman with a term gestation, the clinician has the choice between induction of labor and expectant management, not spontaneous labor. Expectant management of the pregnancy involves nonintervention at any particular point in time and allowing the pregnancy to progress to a future gestational age. Thus, women undergoing expectant management may go into spontaneous labor or may require indicated induction of labor at a future gestational age. Randomized controlled trials suggest that elective induction of labor at 41 weeks of gestation and beyond may be associated with a decrease in both the risk of cesarean delivery and of meconium-stained amniotic fluid. The evidence regarding elective induction of labor before 41 weeks of gestation is insufficient to draw any conclusions. There are concerns about translation of such findings into clinical practice.

Avoidance of cesarean delivery, fetal overgrowth, shoulder dystocia, and prevention of stillbirth are the main indicators for labor induction in pregnant diabetic patients. Induction of labor in mothers with diabetes mellitus is widely advocated and practiced.[14–16] Data pertaining specifically to labor induction in diabetic pregnancies are scarce. Kjos et al.[17] assessed whether a program of expectant management of uncomplicated pregnancies in mothers requiring insulin in gestational or pregestational diabetes reduces the incidence of cesarean birth. The expectant management did not reduce the incidence of cesarean delivery. Furthermore, there was an increased prevalence of large-for-gestational age infants (23% vs. 10%) and shoulder dystocia (3% vs. 0%). Although the recommendation of the authors was to consider delivery at 38 weeks' gestation, it was not supported by the Cochrane Database evaluation, which concluded that the sample size was too small to make the above recommendation.[18]

In a retrospective study, Lurie et al.[19] concluded that elective induction for uncomplicated gestational diabetes mellitus (GDM) pregnancies does not seem to confer any advantages over expectant management. In another study of insulin use in gestational diabetes, Lurie et al.[20] showed that induction at 38–39 weeks was associated with a significantly lower rate of shoulder dystocia <4% versus 10.2% in historic controls.

In summary, the Cochrane Database[18] concluded that:

> *There is very little evidence to support either elective delivery or expectant management at term in pregnant women with insulin-requiring diabetes. Limited data from a single randomized controlled trial suggests that induction of labor in women with gestational diabetes treated with insulin reduces the risk of macrosomia. Although the small sample size dos not permit one to draw conclusions, the risk of maternal or neonatal morbidity was not modified. Women's views on elective delivery and on prolonged surveillance and treatment with insulin should be assessed in future trials.*

Today, when elective delivery in general and delivery by demand (cesarean delivery or induction) are creating a new trend, the obstetrician, in his decision-making capacity, needs to take into consideration that the success of labor induction is largely dependent on the state of the cervix, which is often unripe at the

time induction is undertaken. The inescapable fact that cervical status is the most important predictor of success led to the development of scoring and predictive systems to assess the inducibility of the cervix; these in turn led to the search for methods to increase cervical compliance.

Induction of labor undertaken with an unfavorable cervix is associated with high failure rates, prolonged labor, a high incidence of cesarean delivery, and an overall increase in maternal-fetal morbidity.[21] Although spontaneous labor has been well characterized, little of practical value is known regarding induced labor. Paucity of information exists regarding the efficacy of labor induction using an integrative approach. In 1997, we studied the efficacy, safety, and duration of induced labor using an integrative approach (prostaglandins, amniotomy, oxytocin).[22] The vaginal delivery rate of 80% in our study was compatible with that previously reported by Satin et al.[8] using a different methodology. We concluded that in women who require delivery, regardless of the Bishop score, strong consideration should be given to induction of labor instead of cesarean delivery because the majority of women induced can achieve vaginal delivery.

Although the success rates of labor induction in this study were encouraging, the cesarean rate in patients who are induced is still significantly higher than that encountered in women undergoing spontaneous labor. Similarly, the clinician should not ignore the potential for complications even though the morbidity rate was <2%. On the basis of these issues, the decision to undertake induction of labor should be made by weighing the risks and benefits compared with those of expectant management. Prostaglandins (PG E_2 and synthetic E_1) are currently by far the most widely used pharmacological agents for cervical ripening. The use of prostaglandins for cervical ripening has been shown to reduce total and maximal doses of oxytocin and to significantly reduce induction to delivery intervals. In double-blind, controlled clinical trials,[23–26] the researchers compared the use of vaginally administered misoprostol to placebo for outpatient labor induction in patients with diabetes. They concluded that misoprostol administered vaginally was no more effective than placebo in reducing the need for inpatient labor induction or the induction-delivery interval. The effects of prostaglandin use on cesarean delivery rates have been inconsistent; in the case of PG E_2 preparations, although some studies showed a reduction, most have not shown a significant decrease. Misoprostol (PG E_1) studies show higher rates of vaginal delivery within 24 hours of induction and that it is more effective for labor induction than oxytocin.[25] When compared to other PG or oxytocin, misoprostol did not result in a significant reduction in cesarean delivery rate. Misoprostol remains associated at higher doses (50 μg) with increased tachystole, meconium passage, and meconium aspiration when compared to PG E_2.[23] The use of 25 μg misoprostol appears to be a safer option.[27] Cesarean delivery rates are also increased because of hyperstimulation when compared to PG E_2. Misoprostol is contraindicated in patients with previous cesarean delivery as the risk of uterine rupture is about 6%.[28]

The management of the macrosomic fetus in diabetic mothers deserves special attention. The relationship between birth weight and rate of shoulder dystocia is well documented in the literature. The higher the birth weight, the higher the risk of shoulder dystocia; at birth weights of 4000–4499 g, the risk of shoulder dystocia is as high as 23%, whereas at birth weights of over 4500 g the risk is 20%–50%.[29] The clinical concerns of fetal macrosomia are increased maternal morbidity and fetal morbidity and mortality. Maternal risks include cesarean delivery, postpartum hemorrhage, and vaginal lacerations. The most common fetal injuries associated with fetal macrosomia are shoulder dystocia complicated by clavicular fracture and brachial plexus injury. Also, fetal macrosomia may be associated with significant long-term effects, such as the risk of childhood and adolescent obesity and the predisposition to obesity in adulthood.

The risk of birth trauma associated with vaginal delivery is well documented. Cesarean delivery, on the other hand, confers a significant protective effect with reported odds ratio of 0.01–0.20.[30] Therefore, common sense would dictate we offer prophylactic cesarean delivery to women with macrosomic fetuses in instances when accurate prediction of birth weight is possible.[31] To date, accurate antepartum prediction of fetal weight still eludes us. Extensive reviews have been written on this subject. Sacks et al.[31] studied whether fetal macrosomia can be predicted, and if changing patient management based on that prediction will significantly alter maternal and perinatal outcomes. The authors concluded that sonographic estimates are no more accurate than clinical estimates of fetal weights and that, to date, no management algorithm based on estimates of fetal weight has demonstrated efficacy in reducing the incidence of either shoulder dystocia or brachial plexus injury. O'Reilly-Green et al.,[32] in a study reviewing sonographic and clinical methods in the diagnosis of macrosomia, concluded that clinical decisions about the timing and route of delivery for patients with diabetes should be based primarily on clinical rather than on sonographic estimates of fetal weight.

In our study[33] of shoulder dystocia, we strongly advocated for the need to develop a preventive strategy recommending elective cesarean delivery for diabetic women with fetuses with an estimated fetal weight of ≥4250 g. The study showed that in diabetic women, approximately 80% of the cases of shoulder dystocia with and without trauma can be eliminated by cesarean delivery at estimated fetal weight of 4250 g, with negligible increase in the overall cesarean delivery rate. In contrast, in the nondiabetic group, no definitive weight category was identified as the optimal threshold for cesarean delivery to prevent shoulder dystocia. Rouse et al.[34] analyzed the cost-effectiveness of elective cesarean delivery for macrosomia and found that cesarean delivery of diabetic pregnancies with an estimated fetal weight ≥4000 g is defensible. The American College of Obstetrics and Gynecology considers a planned cesarean delivery for a diabetic woman whose estimated fetal weight is ≥4250–4500 g a reasonable option.[29,35]

GLUCOSE CONTROL DURING LABOR

With the development of new technology such as continuous glucose monitoring, we are able to characterize the true nature of the glycemic profile throughout a 24-hour period. A question that has often been raised is if labor is comparable to exercise and if different stages of labor utilize glucose differently. By answering these questions, we are able to manage fluid administration more efficiently. We studied nondiabetic women during labor. All patients were evaluated using continuous glucose monitoring system (CGMS) for 72 consecutive hours. CGMS measures in subcutaneous tissue interstitial glucose levels within a range of 40–400 mg/dL every

five minutes for a total of 288 measurements/day. The evaluation time frame was from the latent phase until 24-hour postpartum. Eligibility was limited to healthy nondiabetic women ≥37 weeks singleton pregnancy, with no chronic diseases, who did not receive drugs known to have an effect on carbohydrate metabolism (i.e., steroids and β2-sympathomimetics). All participants did not receive fluids containing glucose during labor and had spontaneous vaginal delivery. During the second stage of labor, significantly lower mean blood glucose (MBG) was recorded in comparison to latent and active phases, $P = 0.001$. During the second stage 9/32 of the women had hypoglycemic events (blood glucose <40 mg/dL for more than 10 consecutive minutes) with no alteration in fetal heart rate. MBG during the 24-hour postprandial was significantly higher in comparison to labor and delivery, $P = 0.02$. During normal labor, there is a gradual physiological decrease in glucose levels, which is pronounced during the second stage. Glycemic profile characterization during delivery and early postpartum may be used to define normality in this time frame and to define the degree of deviation from this norm that may be associated with immediate neonatal adverse outcome in a diabetic pregnancy (Figure 38-1).

The goal of intrapartum glycemic control is maintenance of maternal euglycemia. Intrapartum maternal hyperglycemia is directly related to fetal hypoglycemia. Even in the presence of poor antepartum glycemic control, tight control of plasma glucose levels appears to significantly reduce the incidence of neonatal hypoglycemia. Therefore, careful attention should be given to the administration of dextrose solutions and to insulin administration during labor. Several studies showed an association between neonatal-fetal hypoglycemia and increased fetal lactate levels and oxygen consumption with subsequent acidosis and fetal death.[36] The fetal and neonatal hazards increased when 5% dextrose solution was used during labor. Kenepp et al.[37] in a randomized study demonstrated that rapid infusions of ≥25 g glucose is associated with fetal acidosis, neonatal hyperinsulinemia, hypoglycemia, and hyperbilirubinemia. The authors concluded that it seems prudent to limit maternal dextrose infusions before cesarean delivery to 6 g/h, whereas for the patient in active labor, the dose may be greater. Maximum safe doses still have to be established. Jovanovic and Peterson[38] showed that in diabetic women with good glycemic control before labor, insulin requirements decrease to zero during induced active labor and glucose requirements are relatively constant. Other studies[39,40] have shown no decrease in cord pH level with the infusion of 5% dextrose solutions at rates of 125–200 mL/h. As maternal hyperglycemia remains the major cause of neonatal hypoglycemia, the following guidelines are recommended for the intrapartum glycemic management of diabetic women in labor:

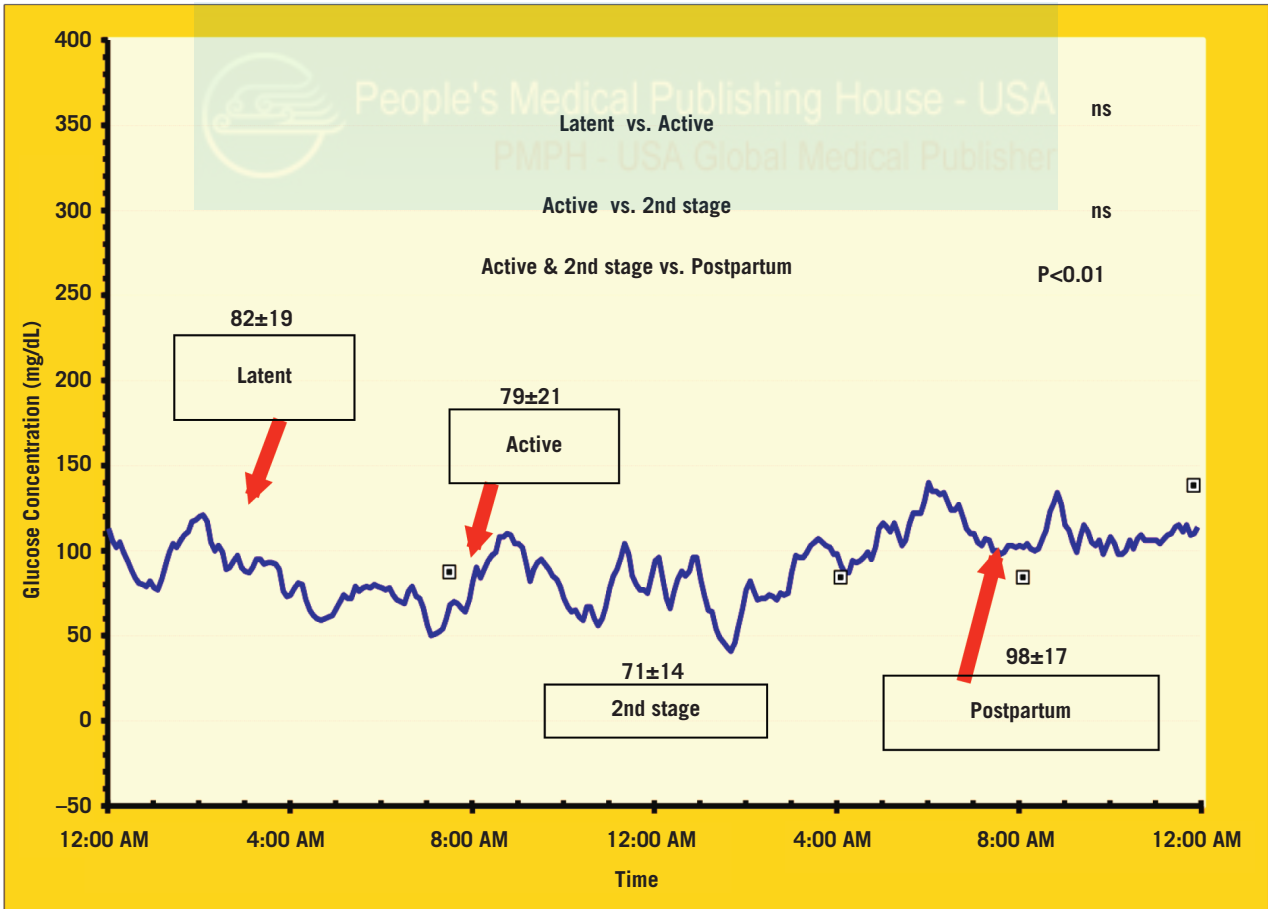

Figure 38-1 Glycemic characteristics during labor using continuous glucose monitoring.

- Maintain blood glucose at 70–90 mg/dL
- Before labor induction or elective cesarean delivery, patients should not eat and/or drink for at least eight hours
- Insulin is administered in the usual dose at bedtime. In patients using the pump, the infusion is continued overnight.
- Withhold the morning dose of insulin before labor induction or cesarean delivery
- Normal saline may be sufficient to maintain glucose control
- Regimens for insulin administration during labor include the following:
  - 10 U of regular insulin in 1000 mL of 5% dextrose solution with an infusion rate of 100–125 mL/h (1 U/h)
  - 15 U of regular insulin in 150 mL of normal saline at a rate of 1–3 U/h
  - Syringe pump at a rate of 0.25–2 U/h.
  - Glucose levels should be checked and documented every 1–2 hours and the insulin administration should be adjusted accordingly
  - Patients who achieved good glycemic control throughout pregnancy, in the first stage of labor might require glucose at an infusion rate of 2.5 mg/kg[38]
  - In the second stage of labor, they might require an increase in insulin administration secondary to increased cathecolamine secretion and muscle action
  - Bolus doses of glucose should be avoided during labor because of an increased risk of neonatal hypoglycemia, fetal hypoxia, and fetal/neonatal acidosis.[37,41]

Postpartum insulin requirements drop significantly. It is recommended to restart patients at $^1/_3$ of the end of pregnancy dose, or recalculate the insulin requirements at about 0.6 U/kg per day based on actual weight. Caution should be exercised in the management of postpartum and nursing diabetic mothers as hypoglycemia appears to be more frequent at these times.

SUMMARY

How to deliver the pregnant diabetic patient is directly related to the why and when to deliver. The risk of stillbirth, large-for-gestational age fetus, macrosomia, and shoulder dystocia remain major concerns in these pregnancies and account for the high rates of labor induction and cesarean delivery. Furthermore, diabetic fetopathy is associated with labor abnormalities and shoulder dystocia.[42] The conduct of labor, labor induction, and augmentation should follow current recommendations.[7,28] Cesarean delivery is a reasonable option for estimated fetal weight of ≥4000 g.[29,33] The goal of intrapartum glycemic control is maintenance of maternal euglycemia to preclude neonatal hypoglycemia.

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