Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research: Workshop Report

Committee on Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research, Linda Giudice, Eileen Santa, and Robert Pool, Editors

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ASSESSING THE MEDICAL RISKS OF HUMAN OOCYTE DONATION FOR STEM CELL RESEARCH

Workshop Report

Committee on Assessing the Medical Risks
of Human Oocyte Donation for Stem Cell Research

Board on Health Sciences Policy
Institute of Medicine

Board on Life Sciences
Division on Earth and Life Studies

Linda Giudice, Eileen Santa, and Robert Pool, *Editors*

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Linda D. Applegarth, The Center for Reproductive Medicine & Infertility, Weill Medical College of Cornell University
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Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the final draft of the report before its release. The review of this report was over-

seen by **Dr. Mary Jane Osborn,** University of Connecticut Health Center. Appointed by the National Research Council and the Institute of Medicine, she was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Preface

Stem cells have the potential to cure common, as well as rare, chronic diseases. They also are the focus of intense basic research to elucidate fundamental biological processes as well as the subject of applied research efforts, such as in testing the efficacy and mechanisms of specific drugs and chemicals. Because of the far-reaching opportunities offered by stem cells, the voters in California, in November 2004, approved Proposition 71, a 10-year, $3 billion program to fund stem cell research under the auspices of the newly formed California Institute for Regenerative Medicine.

This bold program has articulated a strategic plan that includes building facilities in which stem cell research will be conducted, training scientists in the conduct of stem cell research, and developing therapies of stem cell transplantation into people with the goal of improving human health. To accomplish these goals, stem cells from a variety of sources—adult tissues, fetal tissues, gametes, amniotic fluid, human embryos—will be of value in this major program, and a large supply of these is anticipated for eventual, large-scale therapeutic trials and eventually therapies for relief of human suffering from chronic diseases. Human eggs (oocytes) and embryos that may serve as a resource in stem cell research will come from human donors. The task of the Committee on Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research was to organize a workshop and prepare a summary of the current state of knowledge of the medical risks of human oocyte donation for stem cell research.

Human embryonic stem cells are currently derived primarily from unwanted or "surplus" (donated) human embryos from patients who have undergone treatments for infertility. Human embryonic stem cells may also be derived by a process called somatic cell nuclear transfer, in which the nucleus of a somatic cell (i.e., a cell that is neither an egg nor a sperm) is transferred into a human egg as its nucleus. Thus, for human embryonic stem cells, the human egg is a vital component of the process, and these eggs come from the ovaries of women who would choose to donate their eggs (or embryos) for this research effort. Because it is not known with certainty how many unwanted and donated embryos from fertility clinics are available nationally for stem cell research, it is likely that the majority of eggs will come from human donors. The donation process involves stimulation of the ovaries with fertility medications (gonadotropins) and subsequent retrieval of the eggs from a woman's ovaries, usually in an operative procedure requiring light anesthesia.

The California Institute for Regenerative Medicine approached the Institute of Medicine and the National Research Council about convening a committee of experts to ascertain the medical risks of oocyte donation for stem cell research. The committee members are leaders in the fields of human embryology, reproductive medicine, reproductive psychology, women's health, and biostatistics. The group prioritized the issues and recommended a group of experts in the field to attend a workshop to discuss what is known about the medical risks, what needs to be known, and what can be done to reduce the potential risks over time. This workshop was convened on September 28, 2006, in San Francisco.

The workshop focused on potential acute and chronic risks of oocyte donation for stem cell research. The acute risks discussed were ovarian hyperstimulation syndrome and surgical, infectious, and anesthetic risks; and potential chronic risks, including breast, ovarian, and endometrial cancer; future fertility; and psychological risks. The workshop included attendees with expertise and interest in the field, and a dialogue ensued among the speakers, the committee members, and the attendees in the audience. The event was also webcast so that interested members of the public could participate in the proceedings.

This report describes scientific and clinical studies and the data derived from them, on which the risks were assessed as well as the methodological and study limitations that have made definitive risk assessment, for some risks, difficult to ascertain. The report contains neither speculation nor information outside what was discussed at the work-

shop, and it does not contain recommendations. We hope that the report will serve as a resource on the state of the knowledge of acute, chronic, and potential risks associated with oocyte donation for stem cell research for the California Institute for Regenerative Medicine and others wanting more information about this interface between science and medicine.

Linda C. Giudice, Chair
Committee on Assessing the Medical Risks
of Human Oocyte Donation for Stem Cell Research

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Summary

Stem cell treatments have the potential to revolutionize medicine. It could be possible to develop stem cell–based treatments for chronic heart disease, Type I diabetes, and Parkinson's disease, for example, and to use stem cells in the healing of spinal cord damage, the brain damage caused by a stroke, or the damage to heart muscles caused by a heart attack.

In California, in recognition of this potential, Proposition 71 set up a 10-year, $3 billion program to build facilities for stem cell studies and to fund research with the ultimate goal of helping to develop therapies based on stem cells.

This research, however, would require a steady supply of stem cells, particularly human embryonic stem cells. Those embryonic stem cells are collected from developing human embryos that are created from eggs—or oocytes—harvested from the ovaries of female donors.

The oocyte donation process is not without its risks to the donors, and the California Institute for Regenerative Medicine contracted with the National Academies to assemble a workshop that would bring together experts from various areas to address the questions of what is known about these risks, what needs to be known, and what can be done to minimize them. In response, the National Academies formed the Committee on Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research that held a workshop in San Francisco on September 28, 2006, devoted to those issues. This report is a summary and synthesis of that workshop.

The report summarizes the views expressed by workshop participants, and while the committee is responsible for the overall quality and accuracy of the report as a record of what transpired at the workshop, the views contained in the report are not necessarily those of the committee.

THE RISKS OF OVARIAN STIMULATION

In order to increase the number of eggs that can be retrieved from a single donor, the donor normally takes a regimen of hormone shots, that is, fertility drugs. These hormones will generally cause 10 to 20 eggs—instead of the usual single egg—to mature in the ovaries at the same time. The drugs also have a variety of potential health effects, some minor and some potentially major.

The most prominent side effect of this ovarian stimulation is ovarian hyperstimulation syndrome (OHSS). Its symptoms include increased ovarian size; nausea and vomiting; increased permeability of the blood vessels, leading to an accumulation of fluid in the abdomen; breathing difficulties; hemoconcentration, or an increased concentration of red blood cells; kidney and liver problems; and, in the most severe cases, blood clots or kidney failure. Data from women taking fertility drugs in order to undergo in vitro fertilization (IVF) show that only a very small percentage—about 0.1 to 0.2 percent—experience what is classified as severe OHSS, and a much smaller percentage suffer truly dangerous complications. For example, about 1.4 of every 100,000 women undergoing an IVF cycle experience kidney failure.

The OHSS risks for egg donors are expected to be much lower than the OHSS risks calculated from women involved in IVF. The reason is that a large percentage of the severe complications of OHSS seen in IVF patients are linked to hormonal changes in a woman's body that accompany pregnancy. Since oocyte donors do not get pregnant in the cycle in which they donate their eggs, they can be expected to have many fewer side effects than IVF patients.

There is also concern that the use of fertility drugs may lead to an increased risk of hormone-dependent cancers—in particular, breast, ovarian, and uterine (endometrial) cancers. Epidemiological studies of this issue must be interpreted carefully, because infertile women generally are at higher risk for these cancers than women in the general population, so the increased risk due to infertility must be separated from any possible increased risk caused by fertility drugs. The evidence to date is limited, but does not support a relationship between fertility drugs and an increased prevalence of breast or ovarian cancer. More research is required to examine what the long-term impact fertility drugs may be on breast and ovarian cancer prevalence rates. For uterine cancer, the numbers are too small to achieve statistical significance, but it is possible that fertility drugs may cause some increased risk of uterine cancer.

Questions have also been raised about the possible effects of ovarian stimulation on a woman's long-term fertility. Presently there is no evidence, either from studies of women who have taken fertility drugs or from what is known about ovarian physiology, that ovarian stimulation may impact a women's long-term fertility.

THE RISKS OF EGG RETRIEVAL SURGERY

Removing the mature eggs from a donor requires surgery—the insertion of an aspirating needle through the wall of the vagina and into the ovary—that is done under anesthesia. Both the surgery and the anesthesia carry certain risks.

Experience with IVF patients shows that the risks are low. One study of several hundred thousand surgeries found, for example, that only 0.002 percent of the women had complications that required surgery to correct. Complications due to infection are also rare and apparently can be avoided almost completely if proper aseptic techniques are used.

Ovarian torsion, in which an ovary twists around its supporting ligament and cuts off its blood supply, is another rare complication in women undergoing IVF. However, it is associated mainly with women who have become pregnant via IVF, so it should be even rarer among research oocyte donors.

In general, consideration of the risk factors for surgical complications—including previous surgeries, a history of pelvic inflammatory disease, endometriosis, and pelvic adhesions—implies that egg donors would be anticipated to have much lower risks from surgery than has been the experience with women undergoing IVF.

Similarly, the risks from anesthesia for oocyte donors should be very low. Anesthesia in general is very safe today, with deaths occurring once in 200,000 to 300,000 cases. It should be even safer for donors, because few of the factors that increase the risks of anesthesia apply to them.

Finally, there are no data to suggest that egg retrieval surgery poses any risk to a woman's future fertility.

THE PSYCHOLOGICAL RISKS OF OOCYTE DONATION

The psychological risks for egg donation for research may differ from donation for reproduction, primarily because of different motivat-

ing factors for donation and different end uses of the donated eggs. When a woman chooses to donate her eggs for use in IVF or scientific research, it is a very personal decision, one with a variety of psychological implications and consequences. The psychological risks fall into three categories: issues associated with the screening process, problems surrounding the donation procedure itself, and the post-donation adjustment to the donation.

The main risk in the first category is that the screening process may reveal some previously unknown psychological or medical condition that disqualifies the woman from donating. This can be uncomfortable or psychologically threatening to the applicant.

During the donation process itself, some women report mood swings and irritability caused by the fertility drugs, pain caused by the injection, and anxiety in anticipation of the surgical procedure. The issues generally disappear after the procedure is complete.

Finally, after the donation, the main psychological issues are related to worries about future fertility and concerns about children conceived from the eggs. The latter will not be an issue for research donors, and the former is best dealt with by having more and better research done about the risks of oocyte donation, so that donors will have a realistic assessment of the risks associated with their donation.

DIRECTIONS FOR THE FUTURE

One of the most striking facts about in vitro fertilization is just how little is known with certainty about the long-term health outcomes for the women who undergo the procedure. There are no registries that track the health of the people who have taken part in IVF, and much of what is known about the risks for women participating in IVF may not be directly applicable to oocyte donors. Research donors, for example, are likely to be drawn from a much broader range of women than IVF patients, who tend to be primarily Caucasian women in middle to upper socioeconomic groups.

Thus it will be important in the coming years to accumulate extensive health data for women whose eggs are harvested and to monitor them for long-term effects. With more data it will be possible to quantify the various risks of oocyte donation much better than can be done today and to put numbers to the risks that a donor may face.

One of the most important challenges facing those collecting oocytes for research will be to minimize the risks for donors. Two strategies will be particularly important in this effort. The first is to identify, through a screening process, which potential donors have particular medical and psychological risk factors and to exclude them from the donor pool, since their risk for complications is higher than normal. The second is to tailor the donation process to the individual patient, modifying the procedures as necessary to keep each patient's risks to a minimum. For example, it is possible to minimize the risk of OHSS by monitoring the number of eggs maturing in a woman's ovary and then modifying the hormone treatment accordingly, so that she does not develop too many eggs at one time.

Finally, it makes sense to look for alternative sources of oocytes that do not depend on putting women volunteers through ovarian stimulation and retrieval surgery. It may be possible, for example, to develop ways to bring immature and partially mature eggs to maturity in vitro, which would increase the number of available oocytes without increasing the number of donors. Or, with the development of the proper retrieval and storage techniques, it might be possible to retrieve oocytes from cadavers in much the same way that organs are retrieved from the bodies of people who have signed organ donation cards. At this point, it is uncertain how many oocytes may ultimately be available from such alternative sources.

1

Introduction

It is widely understood that stem cell treatments have the potential to revolutionize medicine. Doctors and medical researchers think, for example, that it could be possible to develop stem cell–based treatments for such diseases as chronic heart disease, Type I diabetes, and Parkinson's disease. Stem cells could also prove valuable in repairing various injuries, such as spinal cord damage, the brain damage caused by a stroke, and the damage to heart muscles caused by a heart attack. And cell lines created from stem cells could be used in the testing of drugs and in various types of biomedical research.

Because of this potential, in 2004 California voters approved Proposition 71 to set up a 10-year, $3 billion program to fund research on stem cells. Under the direction of the California Institute for Regenerative Medicine, this program will pay to build facilities for stem cell research and will fund doctors and scientists to carry out research with the ultimate goal of helping to develop therapies based on stem cells.

For this research to move forward, however, will require a steady supply of stem cells, particularly human embryonic stem cells. Those stem cells are collected from developing human embryos created from eggs—or oocytes—harvested from the ovaries of female donors. Thus much of the promise of stem cells depends on women choosing to donate oocytes to the research effort.

The oocyte donation process is not without risk, however. Donors are given doses of hormones to trigger the production of more eggs than would normally be produced, and this hormone treatment can have various side effects. Once the eggs have matured in the ovary, they must be

retrieved via a surgical procedure that is typically performed under anesthesia, and both the surgery and the anesthesia carry their own risks. Furthermore, given the very personal nature of egg donation, the experience may carry psychological risks for some women as well.

With this in mind, in 2006 the California Institute for Regenerative Medicine contracted with the National Academies to organize a workshop that would bring together experts from various areas to speak about the potential risks of oocyte donation and to summarize what is known and what needs to be known about this topic. The Committee on Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research was formed to plan the workshop, which was held in San Francisco on September 28, 2006. This report is a summary and synthesis of that workshop.

SOURCES OF STEM CELLS

Stem cells are the body's resource for all other types of cells. That is, stem cells are unspecialized cells that can self-replicate and give rise to specialized types of cells, from neurons to white blood cells. Stem cells come in several varieties, including embryonic, fetal, and adult stem cells, but most of the interest in possible medical applications has focused on: embryonic stem cells and adult stem cells. Embryonic stem cells can give rise to any type of cell in the body, whereas adult stem cells are generally more limited, giving rise to only certain types of cells, depending on where in the body they are located. Although adult stem cells may have many important therapeutic uses, embryonic stem cells are generally considered to have more potential at this time, in large part because it is relatively easier to grow large numbers of embryonic stem cells in a cell culture. And, in particular, Proposition 71 gives priority to human embryonic stem cell research.

As Linda Giudice, the committee chair, explained in her introductory remarks at the workshop, human embryonic stem cells are generally collected from the inner cell mass of the blastocyst. A blastocyst is a spherical preimplantation embryo containing 200 to 250 cells. It consists of an outer layer of cells, the trophectoderm, and an inner fluid-filled cavity (blastocoel) containing an interior cluster of cells called the inner cell mass. It is the inner cell mass from which embryonic stem cells are derived.

The embryos used as a source of embryonic stem cells can be created in two ways (see Figure 1-1). The most common way—and, indeed, the only proven way with human embryos at this point—is by in vitro fertilization (IVF), in which an egg is fertilized with sperm cells in a culture dish. A second technique, called somatic cell nuclear transfer, works by replacing the nucleus of the egg with the nucleus of a somatic cell (i.e., a cell that is neither an egg nor a sperm) from the same or another person. Since the nucleus of a cell contains its nuclear DNA, an egg used for somatic cell nuclear transfer has all of its DNA (except for that associated with another cell structure called mitochondria) from the person donating the somatic cell and none from the egg donor. This technique may one day make it possible to grow tissues that are genetically nearly identical to a donor—allowing doctors, for example, to create replacement organs that would not be rejected by a patient's body—but at this point no one has succeeded in making somatic cell nuclear transfer work with human oocytes.

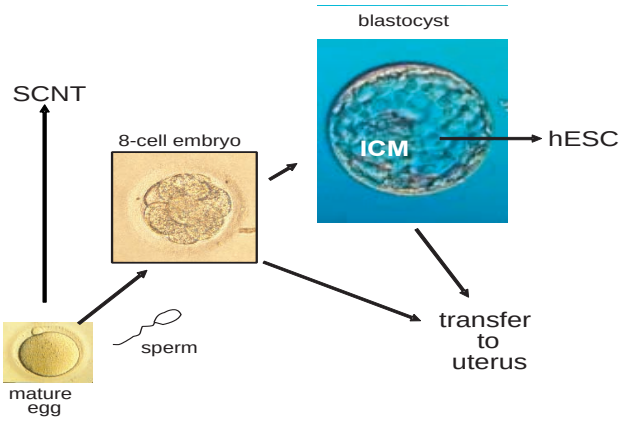

FIGURE 1-1 The procurement process and options for oocytes and embryos for research.
Note: Retrieved oocytes can be inseminated with sperm and subsequent embryos can be transferred to a women's uterus at the 8 cell stage or at the blastocyst stage. Alternatively, oocytes can be used for research and undergo somatic cell nuclear transfer (SCNT). Also, the inner cell mass (ICM) of the blastocyst can be used to derive human embryonic stem cell (hESC) lines.

The major source of human embryonic stem cells to date has been excess IVF embryos that are donated by couples who have completed their treatment for infertility. In cases in which female patients cannot produce their own eggs, these embryos are made using donated eggs from other women. If stem cells are to be made by IVF purely for research, however, and not as a part of infertility treatment, this would necessarily require the donation of eggs. To make stem cells by nuclear transfer would also require the donation of eggs. So research on human embryonic stem cells may eventually demand a supply of eggs that are donated by women for research purposes.

EGG DONATION

Over the past two decades, millions of women have had oocytes collected for the purpose of assisted reproduction. Most of those women were IVF patients whose eggs were viable but who were unable to achieve a pregnancy for some other reason, such as blocked fallopian tubes or a partner with a low sperm count. But a significant minority of the women having their eggs harvested were not themselves trying to get pregnant but rather were donating their eggs to help another woman get pregnant.

In 2003, the latest year for which statistics are available, the Society for Assisted Reproductive Technology reported that there were 115,392 assisted reproduction cycles, or attempts, at 428 clinics around the United States. Of those, nearly 12 percent—or about 13,000 assisted reproduction cycles—involved oocytes provided by egg donors.

Whether a woman's eggs are to be harvested for her own infertility treatment or for donation to another woman—or for research—the donation process is the same. The woman self-injects hormones (gonadotropins) to stimulate the growth of ovarian follicles, plus a gonadotropin-releasing hormone (GnRH) agonist to block the normal surge of luteinizing hormone (LH), which could cause the woman to ovulate before the physician retrieves the eggs. In many instances, GnRH agonists are administered a week before stimulation to control the stimulation cycle and avoid a spontaneous LH surge. A woman subsequently self-injects the hormone human chorionic gonadotropin (hCG, similar to LH) to effect egg maturation. When the eggs are ready, the woman is brought into surgery, where she receives intravenous sedation, after which a transvaginal probe is placed in her vagina. A hollow needle emerges from the probe,

travels through the back of the vagina and into the ovary, where, under the guidance of ultrasound technology, the eggs are aspirated. Typically, a woman who has undergone the usual hormone treatment will have a dozen or so eggs that can be collected.

Once the oocytes have been retrieved, they are prepared for fertilization. Each egg is placed in a culture medium along with prepared sperm cells and incubated for about 18 hours. At the end of this time, the eggs have been fertilized, and they are put into a growth medium for another 1-2 days, until they have reached the four- to eight-cell stage. At this point, they can be transferred into the woman's uterus, although a number of assisted reproduction facilities wait another two days until the fertilized embryo has reached the blastocyst stage, with approximately 100 cells. At this stage, the embryo can be used for the collection of embryonic stem cells from the blastocyst's inner cell mass.

POTENTIAL RISKS

Years of experience with assisted reproduction have identified a number of potential risks associated with egg donation (see Box 1-1), which fall into three main categories. The first category of potential risks arises from the hormone regimen that women are given to stimulate egg production. The risks include ovarian hyperstimulation syndrome; breast, ovarian, and endometrial cancers; and perhaps problems with long-term fertility. The second category is associated with the surgical procedure, including the anesthesia, and involves many of the same issues that anyone having surgery faces. The third set of potential risks is psychological in nature and includes anxiety, mood swings, and post-donation adjustment.

BOX 1-1
Potential Risks of Oocyte Donation

Acute Risks
Ovarian hyperstimulation syndrome
Surgical
Anesthetic
Psychological

Long-Term Risks
Breast, ovarian, and endometrial cancers
Future fertility

The workshop panelists were asked to discuss these potential risks, evaluating the seriousness of each and discussing the uncertainties involved in each. Dr. Giudice summarized the issues before the committee as "what is known, what needs to be known, and what can be done to reduce the potential risks over time." The panelists' answers to those questions are described in the pages that follow.

2

Potential Risks Associated with Hormone Treatment

Louise Brown, born on July 25, 1978, was the world's first baby conceived via in vitro fertilization (IVF). And the egg that produced Louise Brown was created in her mother's body in a completely natural way, without medications from the doctors who were helping Lesley Brown conceive.

Although Louise Brown's birth is proof that it is possible to harvest an egg from a woman and fertilize it without the use of fertility drugs, this approach is inefficient. An egg must mature, must be retrieved and fertilized, then the resulting embryo must divide and grow in the laboratory, and finally it must implant in the uterus. At each stage, the process may be compromised, resulting in a small chance of success in each IVF cycle. For this reason, in the 1980s assisted reproduction specialists began treating the prospective mother—or the egg donor, if the eggs are coming from a woman other than the mother—with a series of hormone injections designed to increase the number of eggs that come to maturity in a given cycle. Thus, multiple eggs could be retrieved at one time with greatly improved chance of a successful outcome.

Today doctors have had two decades of experience with the use of hormone treatments to maximize the number of eggs that can be harvested from a woman, and they have become quite proficient in the production of oocytes. During that time they have also worked to improve the safety of the procedure and decrease the potential risks. Despite these improvements some risk will remain, because hormones have a powerful effect on the body—they could not increase egg production so dramatically if this were not true—and anything with a powerful effect on the body has the potential for harmful side effects as well.

Experience suggests that there are three main risks associated or potentially associated with the hormone treatment used in ovarian stimulation: ovarian hyperstimulation syndrome, cancer, and effects on future fertility. Each risk has its own characteristics and its own implications for egg donors.

OOCYTE PRODUCTION

To understand the potential risks associated with the hormone therapy used in egg donation, one must first understand the hormone therapy itself. And that, in turn, requires an understanding of how the body produces eggs, without outside intervention from administrated hormones.

When a baby girl is born, her ovaries contain roughly 2 million oocytes, each encased in a protective covering called a follicle (see Figure 2-1). At this point, all of the follicles are primordial follicles—follicles that have not taken the first steps down the developmental path that leads eventually to mature follicles. And each of these primordial follicles will sit dormant in a woman's body for as long as 50 years or more, waiting for a signal—researchers are still not sure exactly what that signal is—that will cause that follicle to leave the primordial pool and begin slowly to mature.

Whatever that trigger is, throughout a woman's life there is a steady exodus of these follicles from the developmental pool and down the developmental pathway that will lead eventually—if the follicle survives—toward maturity and ovulation. But only a very few survive, as noted at the workshop by Nicholas Cataldo, formerly an assistant professor of obstetrics and gynecology at Stanford University School of Medicine. At the time of a woman's first menstrual period, she still has 400,000 or so of these primordial follicles, and by the time of menopause they are almost all gone—indeed, it is their absence that triggers menopause—which implies an average attrition of about 1,000 follicles a month. That attrition, Dr. Cataldo said, can occur anywhere along a follicle's developmental path, from its first step as a primary developing follicle, through its secondary follicle stage, and on to its final stage as an antral follicle. It is the antral follicle that, under the influence of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), will grow into a large mature follicle with a mature oocyte in its fluid core.

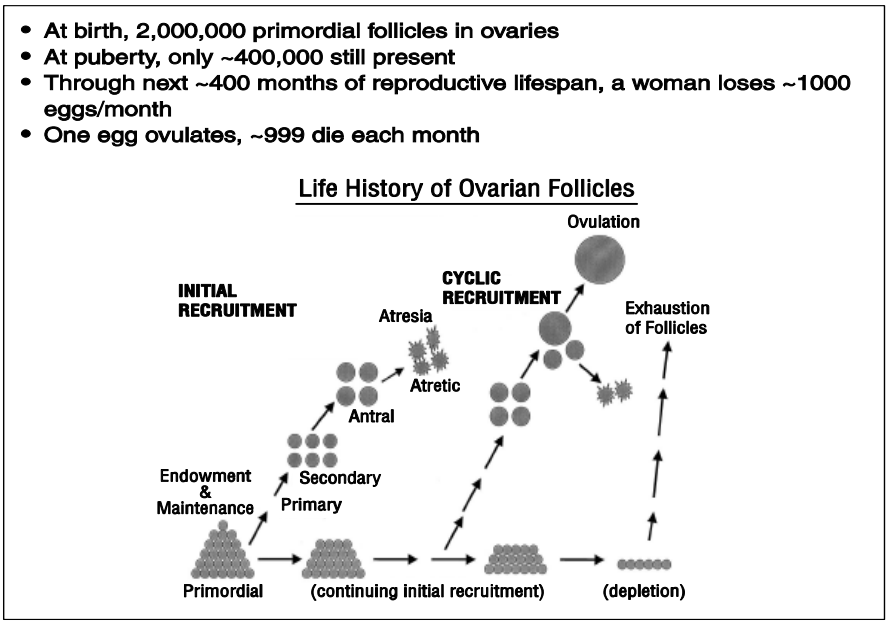

FIGURE 2-1 Follicle/egg number through the life span.
SOURCE: McGee and Hsueh, 2000.
Reprinted with permission from McGee, EA, Hsueh, AJWß. 2000. Initial and cyclic recruitment of ovarian follicles. *Endocrine Reviews* 21(2):200-214. Copyright 2000, The Endocrine Society.

Each month at the onset of the menstrual period, between 10 and 20 follicles will normally reach the antral stage, at which they are ready to grow into mature follicles under the influence of those hormones. Hundreds of other follicles that started down the developmental path at approximately the same time have regressed and have been reabsorbed by the body in the process known as atresia.

Once at the antral stage, the follicles require a certain level of FSH to survive and grow. In prepubertal girls and women taking birth control pills, without high enough levels of FSH to enable them to grow, the small antral follicles remain dominant. In a normally cycling woman, however, FSH levels begin to rise at the start of each menstrual cycle, and, under that influence, the antral follicles begin to grow. One of them will generally be slightly ahead of the others in its development, which gives it the advantage of being slightly more sensitive to FSH, which in turn causes it to grow faster than the other follicles and widen its lead.

This lead follicle is termed the "dominant follicle," Cataldo said, because it acts as the dominant force in the ovary. "It basically makes the smaller ones die," he said, and it does this by producing estradiol and possibly inhibin B as well, both of which are hormones that signal the pituitary gland to cut back on its production of FSH. With less FSH arriving in the ovaries, the smaller follicles do not have enough of the hormone to keep developing and avoid atresia. The dominant follicle, in contrast, is able to survive because of a mechanism that increases its sensitivity to FSH and allows it to keep growing with less FSH than the other follicles need. This process of selecting a single dominant follicle is the reason that women tend to ovulate only one egg per cycle, Cataldo explained. This limit is known to biologists as the ovulatory quota, and it is different from species to species. For example, pigs generally have litters of 6 to 12 piglets; and cows typically have 1 or, at most, 2 calves.

OVARIAN STIMULATION

Although only the dominant follicle survives to produce an oocyte in a normal monthly cycle, the other antral follicles can also survive and grow if there is enough circulating FSH. This is basic of the hormone therapy used to stimulate the ovaries and increase the number of oocytes that a woman can provide for assisted reproduction or for research.

The standard hormone therapy involves daily injections of gonadotropins—most often hormones with an action similar to FSH—beginning on about the third day of menstruation and lasting for about 10 days (see Figure 2-2), after having begun injections of a gonadotropin-releasing hormone (GnRH) to prevent premature oocyte release from the follicles. An alternative is to give the drug clomiphene to induce the body's pituitary gland to release more FSH. With the right amount of hormones, all or almost all of the antral follicles will continue to grow. Occasionally, a GnRH agonist or a GnRH antagonist is added to the mix in order to prevent the body's normal LH surge. Then, when ultrasound shows that the follicles have all reached the proper stage of maturation, with their oocytes ready for ovulation and fertilization, yet another hormone—human chorionic gonadotropin (hCG)—is given. This hormone would normally cause the follicles to ovulate and release their eggs in about 36 hours, but in practice the physician will retrieve the eggs from the follicles before that happens.

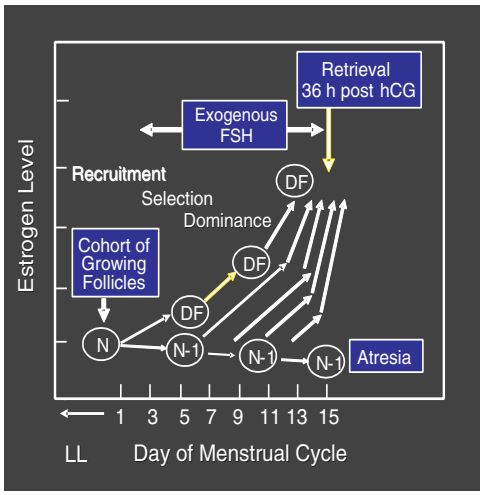

FIGURE 2-2 Follicular growth and selection.
SOURCE: Racowsky (2006). Reprinted with permission from the author.

Thus, as Marcelle Cedars, director of the Division of Reproductive Endocrinology and Infertility at the University of California, San Francisco, noted, hormone therapy acts to increase the number of available eggs in a way that is much different from how most people assume it works. "While we talk about stimulating donors, we really misspeak," she said. "I have to explain this to patients quite frequently because the implication is that I can make more eggs be there. The reality is what I'm doing is rescuing those eggs from the antral stage forward that would otherwise undergo atresia." And this, she noted, is an important point in understanding what the potential risks are for women who undergo this hormone treatment.

POTENTIAL RISK OF OVARIAN HYPERSTIMULATION SYNDROME

The most common side effect of the use of fertility drugs is what is called ovarian hyperstimulation syndrome (OHSS), Dr. Cedars said. "In essence," she explained, "ovarian hyperstimulation is exaggeration of a desired response. We want to override a mechanism of getting a single egg." A key factor in the development of OHSS is the administration of

the ovulation-inducing hCG; the syndrome will not occur in the absence of hCG.

Doctors diagnose OHSS by looking for a characteristic collection of symptoms. The ovaries are increased in size, and there may be gastrointestinal symptoms, such as nausea. The blood vessels become more permeable, and this leads to an accumulation of fluid that can collect in the abdomen and cause discomfort. If there is enough fluid buildup, the abdomen can become somewhat distended, which may lead to pressure on the diaphragm, which in turn can lead to shortness of breath and labored breathing. Blood volume may decrease, leading to an increased concentration of red blood cells.

Traditionally, cases of ovarian hyperstimulation syndrome were classified as mild, medium, or severe (see Box 2-1), Dr. Cedars said, but today the mild cases are not generally considered to be ovarian hyperstimulation syndrome at all, but rather a normal response to the hormone treatment. "It's probably true that most women who undergo ovarian stimulation will have some mild symptoms of hyperstimulation," she explained. Indeed, about 10 percent of women feel a lower abdominal or pelvic pain—called *mittelschmerz*—about halfway through a normal menstrual cycle, even though they have only a single follicle growing to its full size of about 20 millimeters. Since ovarian stimulation generally results in 10 or more follicles growing to a large size, it is not surprising that some women should feel pain as their ovarian capsule stretches to accommodate the multiple follicles that are growing. The mild cases generally have no serious complications, resolve themselves spontaneously, and are quite common in women after hormone treatment.

Moderate cases of ovarian hyperstimulation syndrome are characterized by more than minimal discomfort, a significant fluid buildup (ascites) in the abdomen, leading to a shortness of breath (dyspnea) because of the pressure on the diaphragm, and nausea and vomiting. The blood volume and concentration of red blood cells are normal, however, and the patients are usually handled on an outpatient basis.

Serious cases are relatively rare—about 100 to 200 cases for every 100,000 stimulation cycles—but they are the ones that are most worrisome to assisted reproduction specialists (Schenker and Ezra, 1994; Budev et al. 2005). They in turn are divided into three categories: A, B, and C (see Box 2-2).

BOX 2-1
Ovarian Hyperstimulation Classification

- Moderate
  - discomfort, abdominal fluid buildup
  - nausea/vomiting
  - normal hematologic profile
- Severe (100-200/100,000 stimulation cycles)
  - Grade A – outpatient treatment
  - Grade B – hospital admission
  - Grade C – serious complication

SOURCES: Schenker and Ezra, 1994; Delvigne, Rozenberg 2002; Budev et al. 2005.

BOX 2-2
Severe Ovarian Hyperstimulation Classification

- **Grade A** severe cases have enlarged ovaries, clearly evidenced abdominal swelling, shortness of breath, nausea and vomiting, but blood chemistry is normal. Patients with Grade A severe hyperstimulation syndrome are generally treated as outpatients.
- **Grade B** is more severe. Enough fluid has been lost from the blood vessels that the concentration of red blood cells is markedly increased. The white blood cell count may be higher than normal. The blood flow to the kidneys may be less than normal, leading to a buildup of creatinine, a breakdown product from the muscles, and a decreased production of urine. These patients must be kept in the hospital and monitored closely.
- **Grade C** patients are those with serious complications, such as a blood clot or kidney failure. They need hospitalization and appropriate treatment.

It is difficult to get good data on how often such serious complications occur, Dr. Cedars said, but there are some studies that offer an indication. A recent study from Finland, for example, found that kidney failure occurred in about 1.4 percent of patients who had severe ovarian hyperstimulation, or about 1 in 100,000 oocyte stimulation and retrieval cycles. Somewhere between 0.78 percent and 2.4 of patients with the severe form of the syndrome experience blood clots. This would translate into about 0.78 to 2.4 cases for every 100,000 stimulation cycles. Other

potential complications, such as adult respiratory distress, are so rare, Dr. Cedars said, that she could find no data to provide an estimate of the rate of occurrence.

It is also difficult to estimate a mortality rate, but, conservatively speaking, death appears to occur at a frequency between once every 450,000 and once every 50,000 egg donation cycles (among women with severe OHSS). The numbers are misleading, however, because they include patients who become pregnant with the eggs retrieved from their ovaries and later form blood clots during the pregnancy.

Generally speaking, Dr. Cedars warned, the data concerning the occurrence of ovarian hyperstimulation syndrome are not particularly good. For example, there are very few prospective studies—in which an investigator watches a large cohort of women from before the time they undergo ovarian stimulation until long enough afterward to know the final outcome. Three prospective studies that had reasonable sample sizes reported a risk for OHSS to be between 2.1 to 4.7 percent.

Without the control that comes from a prospective study, it is difficult to get a good measure of the rate of occurrence, and it is difficult to know what the risk factors were for each patient. And without knowing what the risk factors are, it is hard to identify groups of women who are particularly likely to suffer from ovarian hyperstimulation.

Finally, very few of the studies divide cases of the syndrome into early- and late-occurring classifications. Early cases of ovarian hyperstimulation occur within three to seven days of the injection of hCG given to start the ovulation process, and these early cases are caused by that hCG trigger. The late form of ovarian hyperstimulation, by contrast, occurs 12 to 17 days after the hCG trigger and happens in women who have become pregnant with their own fertilized eggs put back into the uterus after the egg retrieval process. In this case, the hyperstimulation syndrome is triggered by hCG from the placenta released early in the woman's pregnancy.

The distinction between early and late is important, Dr. Cedars said, because the risk of severe complications appears to be about 4 to 12 times higher among women with the late-onset hyperstimulation syndrome. It is particularly important for the issue of donating eggs for research purposes, since these donors will not become pregnant immediately after donating their eggs and thus will not be affected by the late-onset type of hyperstimulation syndrome.

Doctors can use a number of strategies to help egg donors avoid hyperstimulation (see Box 2-3), Dr. Cedars said. The first is simply

to identify potential donors who are at high risk of developing ovarian hyperstimulation and tailor the stimulation to the individual patient's physiology. One risk factor is simply youth: the younger a woman is, the more primordial follicles she has remaining in her primordial pool, and the more antral follicles she will have available for rescue. Thus, to avoid hyperstimulation in younger women, they should receive minimal or mild stimulation. By working from such information as a patient's age, weight, and follicle count, Dr. Cedars said, a doctor can begin with an FSH dose based on those factors and then modify it as necessary. "We monitor during the course of the stimulation to further decrease the dose if too many follicles are developing or the estradiol levels are too high."

A second group of women at high risk are those with ovulatory abnormalities, in particular, women with polycystic ovarian syndrome (PCOS). PCOS is an endocrine disorder that affects 5-10 percent of women and is characterized by irregular or missing ovulation, a higher than usual level of androgens, or male hormones, and multiple cysts in the ovaries. These cysts are follicles that have grown to the small antral stage but, because of abnormal hormone levels, never grew further and do not release an egg. Reproductive specialists have recognized for many years that stimulating these women's ovaries, even in a very mild way, puts them at a high risk for hyperstimulation. And it now appears, Dr. Cedars said, that the at-risk group is larger than this. Even women who don't have all the classic symptoms of PCOS—they may have regular ovulatory cycles, for example—but who have polycystic ovaries are still

BOX 2-3

Ovarian Hyperstimulation Syndrome

Strategies for Prevention

- Identification of the patient at risk
- Individualization of stimulation protocols ("gentle stimulation")
- Decreasing the pool of granulosa cells/follicles
- Using LH or GnRHa as ovulatory trigger
- Modify stimulation protocol
  - Decrease gonadotropin dosage
  - OCP/Lupron/Low dose gonadotropins
- Reduce the ovulatory dose of hCG
- Delay administration of hCG: "Coast"
- Cancellation of cycle eliminates the risk of OHSS
- Withhold hCG administration

at risk for hyperstimulation. Other risk factors include irregular menstrual periods and low body weight.

It is also makes sense to try different modifications of the hCG part of the treatment, she noted, since hCG acts as the trigger for the hyperstimulation. One approach, for example, is to decrease the hCG dose. A second would be to use recombinant LH in place of the hCG. LH has a similar effect to the hCG but has a shorter half-life, so it does not remain in the system as long and therefore might not be so likely to cause hyperstimulation. There is preliminary evidence to suggest that both of these approaches decrease the occurrence of ovarian hyperstimulation.

In summary, Dr. Cedars said, she thinks oocyte donation for research can occur safely. It is not possible to completely eliminate ovarian hyperstimulation, but it is possible to limit its incidence and severity. A strategy for doing that might include excluding women from donating their eggs who have irregular menstrual cycles, who have ovaries with a polycystic appearance, and perhaps even those with high levels of androgens, as well as modifying the hormone treatment regimen to minimize the factors that are known to make hyperstimulation more likely, such as a higher than normal egg follicle count.

POTENTIAL RISK OF CANCER

One of the most serious concerns about ovarian stimulation is that it may increase the chances that a woman will suffer certain types of cancer later in her life (see Figure 2-3). In particular, said Roberta Ness, chair of the Department of Epidemiology at the University of Pittsburgh, there are three types of cancer that would seem to have a plausible biological link to the hormone regimens used in ovarian stimulation: breast, ovarian, and endometrial cancers.

Breast cancer, she noted, is the most common form of cancer among women and the second most common cause of death for women. Ovarian and endometrial cancers are not as common but are still dreaded among women because of their fatality rates.

There are several reasons to be concerned that the hormones used in assisted reproduction might make these three cancers more likely, Dr. Ness said. First, all three of them seem to be affected by hormones. The cells of these three types of cancer all have estrogen receptors, for example, and women who have had children, women who have breast fed, and

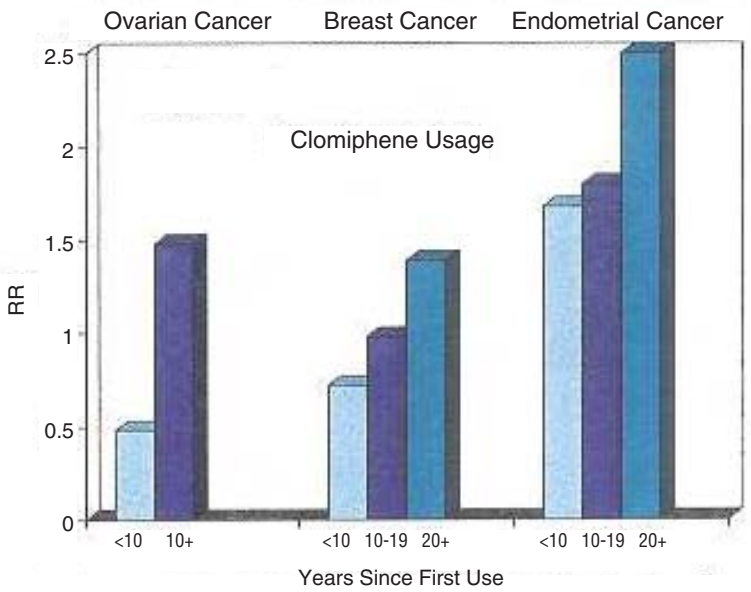

FIGURE 2-3 Clomiphene usage and risk of ovarian, breast, and endometrial cancers.
SOURCE: Louise Brinton, National Cancer Institute, personal communication, 2006.

women who had their ovaries removed are all at a lower risk for these cancers—which implies that hormones have some effect on them. Conversely, women who have a longer than average length of time between their menarche and their menopause are at a higher risk of developing these cancers.

Medical researchers think, Dr. Ness said, that breast tumors grow in response to a combined exposure to estrogen and progesterone. Endometrial cancer seems most affected by estrogen alone. And the risk of ovarian cancer may be increased by an increase in ovulation over a woman's lifetime and by exposure to gonadotropins—i.e., mainly LH and FSH.

Given this, it seems reasonable to suppose that the hormones used in assisted reproduction may well have some effect on a woman's risk of developing these three types of cancer, and the particular effect would depend on the details of the hormone's actions. According to Dr. Ness, "Clomiphene should increase the risk of ovary cancer, perhaps even re-

duce the risk of breast cancer and perhaps the risk of uterine cancer dependent on its impact on the uterus as a selective estrogen receptor modulator (SERM).” The only way to know for sure, however, is to perform studies of women who have taken the hormones in the course of assisted reproduction therapy and compare their risk of cancer with controls who did not have the hormone therapy but who were similar in all other ways. However, that is not as easy as it sounds, Dr. Ness said, and one must be careful in interpreting the studies that have been done.

For example, infertility increases the risk of all three cancers, Dr. Ness said, so a study that compared women undergoing IVF with women in the general population might find the IVF group with a higher rate of cancer—but not because of the fertility drugs they had taken but rather because the infertility that led them to try IVF also made them more likely to develop these cancers. Women who receive assisted reproduction therapy may be more likely than others to get pregnant, and since pregnancy lessens the risk of the cancers, that can have an effect in the opposite direction, making it seem as though ovarian stimulation is less risky than it really is. Different drugs may work via different mechanisms, Dr. Ness pointed out, which means they would have different influences on cancer risk. Nor are all cancers the same. Different types of endometrial cancer, for example, may have different risk factors. All of these complications make it much more difficult to find the real relationship between ovarian stimulation and cancer risk.

With those caveats, Dr. Ness described what is known from epidemiological studies of the cancer risk for women who have had hormone treatment as part of an assisted reproduction program.

In the case of breast cancer, a systematic review of earlier breast cancer studies was published in 2005. Including more than 60,000 women who had undergone ovarian stimulation, it found that most of the 15 studies reviewed saw no significant association between this treatment and the risk of breast cancer.

For ovarian cancer, there have been two published meta-analyses that take data from a number of studies and do a combined analysis. One study in 2002 analyzed 8 case-control studies that included about 5,000 women who had taken fertility drugs and another 7,000 controls who had not. The bottom line, Dr. Ness said, was that the women who had taken fertility drugs had a rate of ovarian cancer basically identical to the rate for the women who had not taken fertility drugs. Thus, existing data do not support an increased risk for ovarian cancer among women who have taken fertility drugs. At this point in time, however, the state of knowl-

edge is not conclusive, and clarification of the exact relationship between ovarian cancer and treatment with fertility drugs will require additional long-term follow-up studies.

Analyzing the data in various ways—differentiating between women who took clomiphene and those who took gonadotropins, for example, and including women who had never been pregnant as the controls—still failed to show any increased cancer risk caused by fertility drugs, with one possible exception. When the cases of ovarian cancer were grouped into borderline cancers and invasive cancers, an increased risk of borderline cancers was seen among women who had taken fertility drugs. But these findings should be interpreted with caution, due to the possibility of surveillance bias. According to Dr. Ness, "Borderline cancers are ones that have a much, much better prognosis," she said, "and they're ones that you would more readily find if you were looking for them." Thus, since women who are undergoing assisted reproduction are more often clinically evaluated by their doctors, it is possible that their asymptomatic borderline tumors may be more commonly detected.

A second meta-analysis of assisted reproductive technologies and ovarian cancers looked not only at case-control studies but also cohort studies. The advantage of the cohort studies, which followed groups of women over a period of time after they took the fertility drugs, is that they make it possible to determine the relationship over time between the hormone exposure and the cancer risk.

For the case-control studies, there did appear to be a 50-percent increase in risk for ovarian cancer among the women who had undergone ovarian stimulation—but only when the control group was the general population. When only infertile controls were used, which is the more appropriate comparison, no increase in risk could be seen at all. And in the cohort studies, there was no increased risk at all. "All of that leads us to a conclusion," Dr. Ness said, "that there's really not much going on."

As for the relationship between fertility drugs and uterine cancer, there have been very few studies. "People didn't turn their attention to uterine cancer until fairly recently," Dr. Ness explained. A review published in 2005 that analyzed the few existing studies on the subject found that women who had taken fertility drugs did have a higher rate of uterine cancer than the general population. The same study looked at the relationship between clomiphene use and uterine cancer and did control for infertility and other confounders, resulting in what Dr. Ness called "a pretty darn fair analysis." The results indicated a possible increase in risk

with clomiphene use, but there were not enough subjects for the results to be statistically significant.

Looking more closely at the data, Dr. Ness said, there does seem to be some reason for concern. The numbers of women in the analyses are very small, so it is difficult to attain statistical significance for the results, but there are trends that deserve a closer look. With increased dosage, with a greater number of cycles of using the fertility drugs, and with more years since first use, the number of uterine cancer cases seemed to be going up. One study in particular focused just on women who had taken clomiphene and looked at the rates of various cancers. It found that as time elapsed since the treatment, there did seem to be an increase in risk for breast, ovarian, and endometrial cancers, with the highest risks for the endometrial cancers. This is of particular concern, Dr. Ness said, because it raises the possibility that many studies have missed the increased cancer risk because they haven't followed their subjects for enough years.

Dr. Ness summarized what is known about fertility drugs and cancer risk this way: "There's no evidence that fertility drugs elevate the risk of breast cancer. There are a couple of little signals in maybe one study, but if we look overall at the literature, it is not terribly convincing. Infertility, not the assisted reproduction therapy, certainly increases the risk of ovarian cancer. There is no systematic evidence at this point that fertility drugs elevate the risk for invasive ovarian cancer. But for uterine cancer, where the data are too sparse to lead to any conclusion, I think that there's a greater concern. And the final concern is that these effects may not be evident until a longer period of time has elapsed between the exposure, the assisted reproduction therapy, and the cancer."

POTENTIAL LONG-TERM FERTILITY EFFECTS

One of the major concerns that has been raised about the possible risks involved with hormone treatment is that the treatment may have some effect on a woman's long-term fertility. "We've heard a lot about ovarian stimulation as a route to achieving more eggs," Dr. Cataldo said. "The question exists whether this results in a depletion of the woman's egg supply. This is an important question, because if this were true, the retrieval of 20 eggs instead of the ovulation of 1 per cycle for 5 or 10 donation cycles might imply a considerable number of oocytes lost. And one might also worry that this could hasten the onset of age-related infer-

tility and even hasten the onset of menopause. If this were the case, repeated stimulations would be more problematic than one or two donation cycles."

There is strong evidence against this idea, he said. The evidence comes from two sources: what is known about basic ovarian physiology and clinical experience.

As described above, a woman has some 400,000 primordial follicles when she first begins to menstruate, and she loses on average about 1,000 of those each month until she reaches menopause. Of those 1,000 per month, only 10 to 20 reach the stage of antral follicles; the rest die at various stages along the developmental path. Normally only one of the antral follicles completes its development and ovulates, with the rest dying and being absorbed by the body, but hormone treatment can rescue most of those.

The first thing to notice, Dr. Cataldo said, is that, according to the current understanding, ovarian stimulation does not cause a woman to lose any more eggs in a given month than she normally would, as all of the extra eggs made available by the hormone treatment are eggs that were slated for atresia anyway. But is it possible that the hormone treatment might somehow affect the rate at which the primordial follicles develop and so increase their rate of attrition throughout a woman's life, causing her to exhaust her egg supply sooner than she otherwise would? Again, what is known about ovarian physiology suggests that this does not happen.

In particular, Dr. Cataldo said, throughout the entire process of follicular development, the hormones FSH and LH affect the follicle only during the last two weeks of its development. For the rest of the time, from the moment a follicle is pulled out of the primordial pool to the point at which it reaches the antral follicle stage, the development of the follicle is largely independent of those two hormones. And, since these are the hormones that are used in ovarian stimulation, it seems unlikely that the treatment would have any effect on follicular development prior to the antral stage.

Dr. Cataldo summarized: "The biology of follicle development predicts that there should be no reduction of follicle supply through repeat stimulation and hence no increase in infertility resulting from a decrease in egg supply."

Furthermore, clinical experience backs up this conclusion. Dr. Cataldo described two clinical studies of women who had had repeated treatments of ovarian stimulation. The first were women from a Dutch

IVF program who had up to six treatments over a period of up to two to three years. "What you can see here is that the number of oocytes retrieved in successive cycles does not fall off, suggesting that we're not pulling oocytes away from the next cycle each time we do a stimulation, and there doesn't seem to be any attrition in the response."

A study of women from a Spanish IVF program reached a similar conclusion. These women donated eggs from one to nine times with a median of four months between cycles, so some of the women experienced hormone treatments stretching out over as much as three years. "Although the numbers are very small at the high numbers of cycles," Dr. Cataldo said, "if you look at just the first 4 or 5 cycles, there appears to be absolutely no fall-off at all in terms of the ability to recruit roughly 15 or 16 oocytes per cycle from these donors in repeated use."

So as far as either basic ovarian physiology or clinical experience indicates, there is no reason to think that repeated ovarian stimulation poses a risk to a woman's long-term fertility. Still, Dr. Cataldo said, not everything is known on the subject, and there are several potentially important questions that have not yet been answered.

It would be helpful, for example, to have a longitudinal study that followed women who had ovarian stimulation all the way to menopause to find out what their reproductive future holds. Do women who have donated their eggs experience higher rates of infertility? And, if so, are there characteristics among these women at the time of their donation that are predictive of the later infertility? Are certain forms of infertility more common among woman who have donated than among the general population? And the ultimate milestone: Do women who have donated their eggs undergo menopause at an earlier age?

SUMMARY: WHAT WE KNOW ABOUT THE RISKS OF OVARIAN STIMULATION FOR OOCYTE PRODUCTION

To increase the number of eggs that can be retrieved from a donor, the usual strategy is to put the donor through a regimen of hormone shots that (1) keep most or all of the donor's antral follicles continuing down the path to maturation instead of just one; (2) prevent the follicles from ovulating before the desired time; and (3) when it is time, prepare the follicles for the harvesting of the oocytes. The hormones used in this

regimen are known to have or suspected of having a variety of health effects, some minor and some potentially major.

The most prominent side effect of ovarian stimulation is ovarian hyperstimulation syndrome. Its symptoms include increased ovarian size; nausea and vomiting; increased permeability of the blood vessels, leading to an accumulation of fluid in the abdomen; breathing difficulties; hemoconcentration, or an increased concentration of red blood cells; kidney and liver problems; and, in the most severe cases, blood clots or kidney failure. The severe cases affect only a very small percentage of women who undergo in vitro fertilization—about 0.1 to 0.2 percent of all treatment cycles—and the Class C severe, or the most dangerous, are an even smaller percentage. Only about 1.4 in 100,000 cycles leads to kidney failure, for example.

The OHSS risks for egg donors are expected to be much lower than the OHSS risks calculated from women involved in IVF. OHSS occurs at two stages: early, 3 to 7 days after the hCG trigger is used to prepare the eggs for retrieval, and is a result of that trigger; and late, 12 to 17 days after the trigger, and is a result of the new pregnancy in a women who has successfully undergone IVF. The risk of severe complications is about 4 to 12 times higher in late-onset OHSS than in early-onset OHSS. Egg donors, because they will not be getting pregnant after donating their eggs, will not be affected by the late-onset OHSS and thus can be expected to have many fewer side effects than are seen in IVF patients.

Many observers have worried that the use of fertility drugs could lead to an increased risk of cancer—in particular, breast, ovarian, and uterine (including endometrial) cancers. One must be careful in interpreting epidemiological studies of women taking fertility drugs, because all of these cancers are more common in women with infertility, so merely comparing women taking fertility drugs with women in the general population inevitably shows an increased cancer risk. When the analysis is done correctly, accounting for the increased cancer risk due to infertility, the evidence does not support a relationship between fertility drugs and an increased prevalence of breast or ovarian cancer. More research is required to examine what the long-term impact fertility drugs may be on breast and ovarian cancer prevalence rates. For uterine cancer, the numbers are too small to achieve statistical significance, but it is at least possible that fertility drugs may indeed cause some increased risk of uterine cancer.

The last concern is that fertility drugs may affect a woman's long-term fertility. However, there is no evidence, either from studies of women who have taken fertility drugs or from what is known about ovarian physiology, that this is the case. The concern seems to be unfounded.

3

Potential Risks Associated with Egg Retrieval

After the hormone treatment has stimulated the ovaries to produce more eggs, those eggs must be retrieved. The retrieval surgery takes place about 36 hours after the injection of human chorionic gonadotropin (hCG), which signals the follicles to prepare to ovulate. In ovulation, a follicle ruptures and expels the egg from the follicular sac, after which the egg will travel through the fallopian tube toward the uterus. Egg retrieval is timed to catch the eggs shortly before they would start this journey, at a point at which they are ready for fertilization but are still within their follicles and they can easily be found.

To retrieve the eggs, a surgeon places a device into the vagina that pushes a needle through the vagina wall and into the ovary (see Figure 3-1). All of the movements are guided by ultrasound technology. Once the needle is inside the ovary, it is maneuvered to pierce one follicle after another. When the needle is inside a follicle, suction is applied to pull the follicular fluid out through a tube and into a test tube. Floating within the fluid extracted from the follicles will be the target of the procedure: the oocytes.

The surgery, which generally lasts about 30 minutes, is done on an outpatient basis, and the woman usually goes home a few hours after the eggs are retrieved. This procedure is considered to be minor surgery. Nonetheless, it is still a surgical procedure done under anesthesia, and both the surgery and the anesthesia carry potential risks. Several speakers at the workshop described these potential risks and detailed what is known about them.

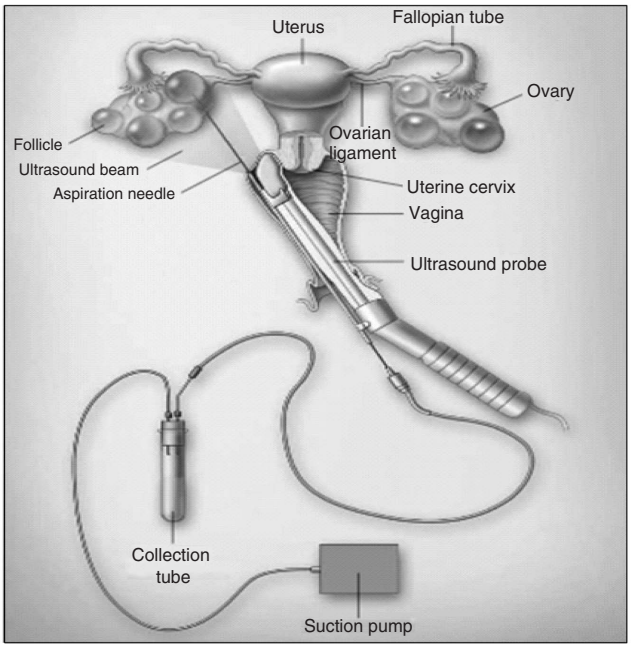

FIGURE 3-1 Oocyte retrieval.
SOURCE: Steinbrook (2006). Copyright © 2006 Massachusetts Medical Society. All rights reserved.

POTENTIAL SURGICAL RISKS

Most of the surgical complications surrounding egg retrieval stem from two basic facts about the surgery: a needle must be pushed through the vagina and into the ovary, and a number of other organs and sensitive tissues lie nearby. The hypogastric artery (also known as the internal iliac artery) runs past the ovary, for example, as does the ureter. The surgeon often finds the ureter right next to the ovary, explained Ana Murphy, chair of the Department of Obstetrics and Gynecology at the Medical College of Georgia, which might put the ureter at high risk for inadvertent damage.

It is difficult to know, however, exactly how often such complications occur, Dr. Murphy said. Although excellent statistics are kept on such things as how many viable eggs each procedure produces, the statistics are not so complete on the complications that ensue during and after

the surgery. Still, there are enough data to get a good idea of what is going on.

Dr. Murphy described the results of a study in Germany that examined the outcome of approximately 380,000 oocyte retrieval surgeries during 2000-2004. There was no information about complications for 28 percent of them, but for the procedures for which there was information, the rate of complications was very low. There was vaginal bleeding in 0.07 percent of the women, intra-abdominal bleeding in 0.05 percent, intestinal injuries in 0.001 percent, and peritonitis, or an inflammation of the peritoneum (the lining of the abdominal cavity) in 0.005 percent. Of all the women who had the procedure, only 0.002 percent—2 in every 100,000—had complications that required surgery to correct.

It is possible, Dr. Murphy said, that these numbers are far too optimistic. "There are those that say that there must be underreporting here, and that has been suggested in the literature. I don't know." But if the numbers are accurate, it is clear that the rate of complications was very low.

A prospective study published in 2006 showed a clearly higher rate of complications, but, again, the rate of serious complications was very low. In a study population of more than 1,000 patients, 2.8 percent experienced some vaginal bleeding, but none required suturing. Indeed, for all but one of the patients, all that was needed to stop the bleeding was the application of pressure; one patient required a tamponade, an absorbent dressing, applied to the wound. Severe pain requiring hospitalization occurred in 0.7 percent of the 1,035 women studied who had undergone oocyte retrieval, and in one case there was an injury to another organ (the ureter), and the patient recovered quickly after a stent was placed in the ureter.

Fewer studies are available that look at the question of infectious complications, and Dr. Murphy described two. In one, published in 1993, 9 patients out of 1,000 had pelvic abscesses after surgery that had to be treated. In a second, published in 2006, there were no abscesses at all. "I was curious as to how there could be such a huge difference," Dr. Murphy said, "so I looked at the materials and methods [in the earlier study]. And what I found was that aseptic technique was not the norm, at least in this institution, and that they cleaned it with saline. They did not do anything other than keep the end of the needle sterile. And so some of this may actually be what happens when you drag in infectious agents with your needle." The implication would seem to be that infectious complications are rare as long as aseptic techniques are used.

Another complication that appeared on occasion was ovarian torsion, which occurs when the ovary twists around on itself, cutting off its blood supply. In a study of 1,500 women who underwent in vitro fertilization (IVF), torsion occurred in 0.13 percent of the cycles. The torsion occurred late, 6 to 13 weeks after the oocyte retrieval, and since the risk of torsion increases with the softening of the ligaments that appears in pregnancy, it seems that torsion is a complication that is mainly associated with women who get pregnant with IVF, according to Dr. Murphy. Later in the workshop, Dr. Zev Rosenwaks, director of the Center for Reproductive Medicine and Infertility at Cornell University, said that torsion can also occur with hyperstimulation in the absence of pregnancy.

Various things can be expected to increase the potential risk of complications for women undergoing oocyte retrieval, Dr. Murphy said. Previous surgeries make complications more likely, for example, because the surgeon finds structures where they're not supposed to be, or else the structures don't move the way they're supposed to move. A history of pelvic inflammatory disease (PID) is also an important risk factor, as are endometriosis and pelvic adhesions. Generally speaking, all of these things are much more likely to be found in women undergoing in vitro fertilization—because of their history of infertility and various efforts to get pregnant—than in women serving as egg donors.

In conclusion, Dr. Murphy said, the data indicate that the potential risks of surgical complications from oocyte retrieval are generally very small. There are very few data that are specific to egg donors—as opposed to infertile women undergoing oocyte retrieval and, later, the implantation of embryos—but all of the evidence implies that the potential surgical risks should be much lower in oocyte donors.

POTENTIAL RISKS OF ANESTHESIA

Besides the potential risks associated with the surgical retrieval, women undergoing oocyte retrieval also face certain potential risks from the anesthesia used to handle their pain during the surgery. Lawrence Tsen, associate professor in anesthesia at the Harvard Medical School, spoke at the workshop about these potential risks.

When discussing the use of anesthesia, Dr. Tsen said, there are three basic subjects to cover: whether anesthesia is needed for a particular pro-

cedure, what form of anesthesia should be used, and what the potential risks are.

To the question of whether anesthesia is necessary for oocyte retrieval, he said, "I would have to answer an emphatic yes." And the reasons for this, he said, come from a consideration of the sorts of pain that a patient faces during oocyte removal.

Three things cause pain during oocyte removal, Dr. Tsen said: the stretching of the perineum when the retrieval tool is inserted, the push of the needle through the vaginal wall, and the insertion of the needle into the ovary. Because of where these pain signals enter the spine, a paracervical block—a type of anesthesia sometimes used during childbirth that involves injecting a local anesthetic on either side of the cervix—would not block all of the pain. Thus an anesthesiologist would need to use something in addition to the paracervical block or else would have to use a spinal anesthetic or some intravenous form of anesthesia or sedation.

Furthermore, Dr. Tsen said, women going through oocyte retrieval have a factor that may make them particularly sensitive to pain. He tested a group of women who were going through in vitro fertilization to see if the higher estrogen levels that they experience made a difference to how their bodies process pain signals. He did this by testing how sensitive they were to two stimuli, cold and pressure, that are processed by the same nociceptors, or sensory receptors, that process pain. He tested the women before they began the IVF process and then again at the time of oocyte retrieval. What he found was that, although the women showed no difference in how they responded to pressure, they were much more sensitive to cold stimuli, and their reaction time to those stimuli was significantly altered. The implication, Dr. Tsen said, was that there is clearly some pain modulation among women undergoing IVF cycles, and it is probably caused by the high estrogen levels.

Given that some form of anesthesia is needed in oocyte retrieval, the next question is what form of anesthesia should be used. Surveys of doctors in the United States, the United Kingdom, and Germany indicate that at least 99 percent of cases of oocyte retrieval rely on intravenous anesthesia or intravenous conscious sedation. Some individuals have tried such alternatives as acupuncture or hypnosis, Dr. Tsen said, but the results have generally not been satisfactory, and often those patients fall back on intravenous conscious sedation. He also said that he has spoken with doctors in other countries, including Canada and France, who report very similar situations, so it would seem that a broad consensus exists as to what sort of anesthesia should be used in oocyte retrieval.

The third question is what potential risks these sorts of anesthesia pose for the patient. There are no statistics that look specifically at the potential risk of anesthesia for patients undergoing oocyte retrieval, Dr. Tsen said, but it is possible to look at the overall risks of anesthesia, see what sorts of factors increase or decrease those risks, and then, by considering what sorts of individuals become egg donors, get a good idea of what the potential anesthesia risks would be for them.

Anesthesia has become very safe over the past couple of decades, Dr. Tsen said. Two of the biggest advances were the development in the 1980s of pulse oximetry and capnography, which allow health care providers to monitor a patient's blood oxygen level and, indirectly, the level of carbon dioxide in the blood as well. Today, thanks in part to such technology but also thanks to better training and guidelines, deaths attributable to anesthesia occur only about once in 200,000 to 300,000 cases. This is comparable to the risk of flying, Dr. Tsen noted, as a person has about one chance in 250,000 of dying each time he or she boards a plane.

Examining the statistics more carefully, it is possible to pick out characteristics that put a person at higher risk from anesthesia, Dr. Tsen said. Those characteristics include being male, being older, being obese, being scheduled for inpatient rather than outpatient surgery, having surgery in an emergency setting, and having a high ASA (American Society of Anesthesiologists) classification. The ASA scheme rates how healthy a patient is on a scale from 1 for a normal healthy patient to 5 for a moribund patient who is not expected to survive 24 hours. Of the characteristics that increase the risk of anesthesia, Dr. Tsen noted, the only ones that might apply to women undergoing in vitro fertilization would be obesity and a higher ASA rating, such as might be the case for a woman who is about to undergo whole-body irradiation to treat cancer and who wants to preserve her fertility by preserving some of her eggs. But for women donating their eggs for research, it seems likely that the only characteristic that would increase the risk of anesthesia would be obesity. "So," Dr. Tsen said, "it suggests to us that anesthetic intervention for this sort of procedure is a very safe intervention."

There are other risks of anesthesia besides death. Some of the major morbidities associated with anesthesia are heart attacks, stroke, pulmonary emboli, and respiratory failure, but, again, they rarely occur. And there are complications that are less threatening, such as difficulty in breathing, that can require the patient to be intubated. When Dr. Tsen performed a study of IVF patients at Harvard Medical School undergoing

anesthesia during oocyte retrieval, he found that such complications as intubation or desaturation—a lowering of the blood oxygen content—were infrequent, but they were more likely in obese patients. Approximately 8 percent of the obese patients experienced desaturation, compared with less than 1 percent of those of normal weight. And 1.7 percent of obese patients required intubation versus 0.1 percent of patients of normal weight.

The bottom line, Dr. Tsen said, is that the potential risks of anesthesia for oocyte retrieval are very low—rare mortality, rare major morbidity, and rare minor morbidity. The one potential risk factor that applies to egg donors and that might put them at more risk during anesthesia is if they are obese, but even then the potential risks remain very small.

POTENTIAL LONG-TERM EFFECTS ON FERTILITY

The final question concerning the potential risks of oocyte retrieval is the surgery's implications for a woman's future fertility. Is her ability to have children in the future threatened in any way by having had this surgery? Nicholas Cataldo, formerly an assistant professor of obstetrics and gynecology at Stanford University, reviewed the evidence bearing on this question for the workshop.

Dr. Cataldo examined two possible pathways by which oocyte retrieval might conceivably affect future fertility. The first pathway begins with the infection and bleeding that, as described above, are occasional side effects of retrieval surgery. These side effects sometimes lead to the need for surgery or to the formation of adhesions, the sticking-together of two adjacent tissues. Both of these results, Dr. Cataldo said, could theoretically lead to fertility problems.

There is little evidence to support this possibility, however. According to one large study, the rate of infection after oocyte retrieval was about 1 in every 200 IVF cycles, and surgery is needed to treat pelvic abscesses in less than 1 in 1,000 IVF cycles. Furthermore, since women have a set of two ovaries and two fallopian tubes, they can remain fertile even if one set is damaged, and there is no evidence that both might be threatened simultaneously by the side effects of retrieval surgery. In one study that examined this particular issue, Dr. Cataldo said, none of the women who had surgery to treat abscesses had them on both sides or lost both fallopian tubes or ovaries. As for adhesions, research has not found a higher rate of adhesions among women who have undergone oocyte

retrieval surgery. Finally, Dr. Cataldo said, since the data involve mainly women who have had fertility problems, it can be expected that the rate of infection among egg donors will be lower than has been seen in the published studies. All of this implies that there is little potential risk of future fertility being threatened in egg donors by infection or bleeding accompanying the retrieval surgery.

The second potential pathway to fertility risk begins with the trauma applied to the ovary by having a needle thrust through its surface. It has been suggested that this trauma could lead to the development of anti-ovary antibodies, and, indeed, several studies have found that women who have undergone oocyte retrievals have a greater prevalence of antibodies to ovarian tissue than those who have not undergone the surgery.

Furthermore, antibodies to ovarian antigens have been shown to be associated with IVF failures and with women having multiple attempts at IVF—a situation that, again, implies that they have had previous failures. It is possible, Dr. Cataldo said, that somehow these antibodies may interfere with sperm binding with or penetrating the oocyte and thus make it harder to fertilize the egg, but there is no evidence that this actually happens. It is difficult to know whether antibodies formed in one IVF cycle have anything to do with the failure of subsequent IVF attempts, or even if the antibodies play any role at all in infertility.

"So both of these potential avenues for risk related to oocyte retrieval have question marks associated with every step of the way," Dr. Cataldo concluded. And whatever risk there may be for women undergoing IVF, the risk would be expected to be somewhat lower in healthy women donating eggs for research.

SUMMARY: WHAT WE KNOW ABOUT THE RISKS OF EGG RETRIEVAL

Once hormone treatment has led the ovaries to create a large number of antral follicles ready to ovulate, a surgeon must retrieve the eggs from the follicles by putting a needle through the wall of the vagina into the ovary and using the needle to aspirate the individual follicles. This surgery must be done with anesthesia, and there are a number of health risks that accompany the surgery and the anesthesia.

The statistics on egg retrieval surgery indicate that the risks of complication are relatively low. One study of several hundred thousand surgeries found, for example, that vaginal bleeding occurred in 0.07 percent

of the women, intestinal injuries in 0.001 percent, and peritonitis in 0.005 percent. Only 0.002—or 2 in every 100,000—had complications that required surgery to correct.

Complications due to infection are rare as well. Although a 1993 study found 9 patients out of 1,000 had pelvic abscesses that needed to be treated, that seems to have been due to a failure to consistently use aseptic techniques. A later study in which aseptic techniques were used found no abscesses that required treatment.

Ovarian torsion is another rare complication in women undergoing IVF—about 0.13 percent of the time, according to one study. According to Dr. Cataldo, this complication seems mainly due to the softening of the ligaments that occurs during pregnancy. Dr. Rosenwaks added that it can also occur due to hyperstimulation, even in the absence of pregnancy.

Various factors increase the risk of complications from retrieval surgery, including previous surgeries, a history of pelvic inflammatory disease, endometriosis, and pelvic adhesions. All these factors are more likely to be found in women undergoing in vitro fertilization than in the general population, which implies that egg donors should have much lower surgical risks than women undergoing IVF.

Patients undergoing egg retrieval surgery generally rely on either intravenous anesthesia or intravenous conscious sedation. In general, anesthesia is safe, with deaths occurring only once every 200,000 to 300,000 cases. Because egg donors have few of the factors that increase the risks of anesthesia, including being male, being older, being obese, having inpatient rather than outpatient surgery, having surgery in an emergency setting, and having a high ASA classification, anesthesia should be even safer for egg donors than it is for surgical patients in general.

There are two main ways that surgery may affect a woman's future fertility—either by bleeding and infection from the surgery leading to adhesions and the need for further surgeries, or else by the trauma to the ovaries causing the creation of antibodies that may make fertilization of an oocyte more difficult—but there is no data supporting either of these possibilities.

4

Potential Psychological Risks

When a woman chooses to donate her eggs for use in the in vitro fertilization (IVF) process or scientific research, it is a very personal decision, one with a variety of psychological implications and consequences. Or as Susan Klock, professor in the departments of obstetrics and gynecology and of psychiatry at Northwestern University, described it, "There is a whole psychology about why a woman does this and what she thinks and feels about being an oocyte donor." And so, in addition to the potential physical risks, the donation process potentially carries with it a number of psychological risks as well.

Those potential risks can be classified into three broad categories (see Box 4-1), Klock said: the psychological aspects of the donor screening process, the psychological aspects of the procedure itself, and a post-donation psychological adjustment to the donation. There have been relatively few studies of the psychology of oocyte donation, she said, and the studies that have been done have generally been small ones with relatively few subjects. Still, it is possible to describe some basic findings about the psychological effects on women who donate their eggs.

POTENTIAL PSYCHOLOGICAL RISKS IN THE SCREENING PROCESS

The egg donor recruitment process is straightforward, Dr. Klock said. An IVF program that is looking for donors or an independent recruiter will place advertisements in university newspapers, on the Internet, and in other places where they can reach large numbers of women in

BOX 4-1
Summary of Potential Psychological Risks

- Psychological risks to donors can occur in the screening, donation, and post-donation time frames
  - Screening–psychological distress from being excluded from donating
  - During donation–psychological side effects from medications and retrieval
  - Post-donation–worry and regret present for a minority of donors
- Long-term follow-up studies of donor health, including psychological health, are needed.

the 21- to 34-year-old age range, which is best for donors. Potential donors then contact the program and are sent forms to fill out providing background information about their medical condition and details about who they are and why they are interested in being an egg donor. Later the recruiter will review that information and bring the potential donor in to talk with her about what it's like to be a donor and to put her through a medical and a psychological screening.

Statistics show that only about 12 percent of women who inquire about being a donor actually complete the screening process and complete a donation cycle, Dr. Klock said (see Figure 4-1).

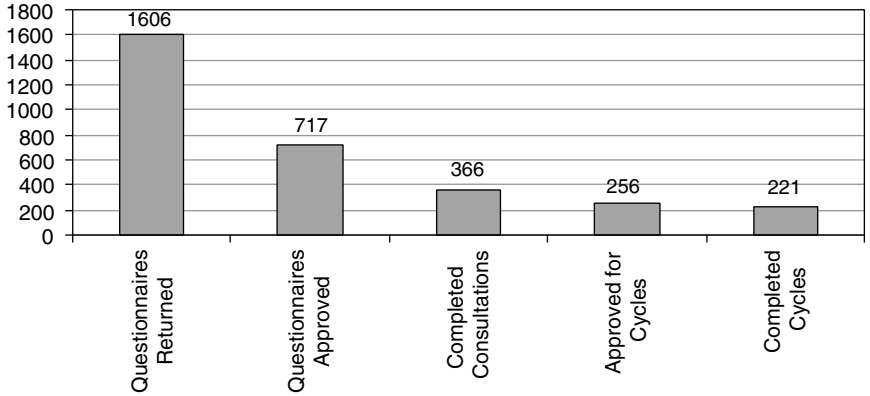

FIGURE 4-1 Impact of donor screening on eventual donation.
SOURCE: Center for Reproductive Medicine and Infertility (unpublished data).

The psychological screening interview typically takes about 60 to 90 minutes, and it is done as a face-to-face discussion. "We put as our purpose for these screenings to give the donor an opportunity to talk about the very complex issues that go along with the decision to be a donor," Dr. Klock said. The American Society of Reproductive Medicine provides guidelines for how to do the screening interviews. The screening is best done, she said, by a licensed mental health professional who has expertise working in assisted reproductive technologies. This expertise is important because a familiarity with the field provides a context that helps the interviewer know which questions to ask.

"When you begin a screening interview," Dr. Klock said, "the first thing that becomes apparent from the donor is the question of motivation. You listen for this in the interview: Why do you want to be an egg donor? And without fail, two ideas come up. The first is, 'I want to help somebody. I know somebody who's gone through infertility. I know somebody who can't have a child. I want to help somebody.'" And the second motivation is usually the compensation. Egg donors in Chicago typically get $7,500 for a single cycle, Dr. Klock said. The compensation is somewhat more in some places, somewhat less in others, but it is substantial enough that it can, when combined with the chance to help someone, make the donation process an appealing opportunity for some women.

Other motivations that potential donors mention include an interest in science, wanting to find out about one's own fertility, and making up for a previous reproductive loss.

In addition to the applicant's motivations for donating, an interviewer will typically cover a number of other standard topics, Dr. Klock said. "We talk about psychosocial issues, the women's reproductive history, her family history, her educational background. And then we also talk about the use and disposition of the oocytes." The interview will also typically include a psychological test, most often the Minnesota Multiphasic Personality Inventory, the MMPI-II. "It's the most widely used psychological test in the United States. It's also the test that's used to screen for professionals in high-risk jobs: airline pilots, firefighters, police officers."

During the interview, the screener is looking for various factors that would exclude the applicant from being allowed to donate eggs. "We're looking for substance abuse or addiction issues, impaired cognitive functioning, or the inability to provide informed consent," Dr. Klock said. In particular, if a woman doesn't really understand the procedure that she's

about to undergo, she is not fully able to give informed consent, and she will be excluded from being a donor on that basis. Furthermore, a women who has suffered from mental illness or who has a family history of mental illness will also generally be excluded. In this case, the reason is not so much a medical or ethical one but rather that very few women undergoing IVF with donated eggs will select a donor with such a history.

One other exclusionary factor is what Dr. Klock referred to as excessive current life stress. "This is kind of a global term," she explained. "If a woman is in the midst of a divorce, or if a woman has just been a victim of a violent crime, this is not a great time for her to be an egg donor."

Studies show that between 2 and 27 percent of potential donors are excluded for psychological reasons, and it is this exclusion that offers the major psychological risk in the screening process. If an applicant is excluded for a psychological reason, the interviewer must explain to her what psychological issues have been discovered and then provide appropriate referrals if there is a problem that needs to be dealt with.

"So the potential risk here," Dr. Klock explained, "is uncovering a previously undetected or undiagnosed psychological problem. That is a very jarring thing for a woman to experience. Sitting in the office with her, talking with her about that, she can tend to feel rejected, inferior. It can be a huge blow to her self-esteem. 'Why? You don't even want my eggs. Oh, I feel terrible.' And that's a very real concern for women from a psychological perspective."

Another potential risk is the possibility of uncovering something in the medical screening that the applicant didn't know about, particularly something that could affect her future fertility. That can also affect a woman psychologically.

POTENTIAL PSYCHOLOGICAL RISKS OF THE DONATION PROCEDURE

The donation procedure itself carries certain potential psychological risks as well, but these tend to be less threatening. They are also temporary, not lasting much past the procedure itself.

One issue is the effect of the hormone injections that the donors give themselves to prepare their ovaries to produce as many eggs as possible. Dr. Klock described a study performed by a pair of doctors who surveyed a group of donors after they had completed a donation cycle. The study found that fully half the donors reported mood swings and irritabil-

ity during the hormone treatment. "This is very similar to what we see among our own IVF patients," she said. "They talk about feeling irritable, rejection-sensitive, lots of crying, lots of low mood, and it does seem to be linked to the use of those medications."

Another issue is concern associated with the egg retrieval surgery. One study of donors conducted by investigators at Dartmouth Medical School found that 83 percent reported high anxiety on the day of retrieval. Besides this anxiety, donors also listed the daily injections, the frequent travel to the clinic, and pain as the most difficult aspects of the donation process itself.

The good news about these potential psychological risks, Dr. Klock said, is that they do not appear to carry over past the donation. Once the surgery is done and the medication is out of a woman's system, the psychological symptoms vanish.

It seems likely, Dr. Klock noted, that the potential psychological risks both here and in the screening process will be the same for research donors as they are for women donating their eggs for reproductive purposes.

POTENTIAL PSYCHOLOGICAL RISKS OF POST-DONATION ADJUSTMENT

There have been at least seven published studies looking at the post-donation psychological adjustment of women who donated their eggs for other women's pregnancies. The studies were generally done as mail-out surveys anywhere from two weeks to seven years after the retrieval surgery, although one survey was done using post-donation exit interviews.

The surveys found that the typical donor is a single, white, high school graduate with some college education who has never had children. "This does not tend to be a very diverse group demographically," Dr. Klock commented.

The psychological risks identified by these studies tend to center on such issues as future fertility and whether a child or children had resulted from the donation. One 1995 study, for example, surveyed 32 donors 18 months after their donations. The donors reported that the most difficult aspects of the donation process itself were refraining from intercourse and the mood swings that they experienced while on the medication. Half of them reported having second thoughts about having donated, and the reasons they gave were concerns about compromising their own fertility

and never knowing if a child resulted from their donation. Or, as Dr. Klock put it, "The thing that is sticking in their minds is, 'In 18 years am I going to be answering the door to one of my offspring?' This is something that tends to stay with them and is a source of concern and sometimes regret." This particular concern will not be an issue for research donors, of course, because their eggs will not figure in a subsequent pregnancy.

In another survey of 24 women done 2 years after donation, 87 percent wanted to know if a pregnancy had resulted, over half were worried about the medical risks, and 17 percent regretted donating. By the same token, a majority were satisfied with their donation, and 42 percent said they would donate again.

And, indeed, although the surveys uncover a minority of women with various concerns, a majority of women seem to be satisfied with their donation experience. In a study done of 24 donors at the Cleveland Clinic contacted 6 and 12 months post-donation, 78 percent reported being very satisfied with the donation process, and 74 percent stated they would be willing to donate again. Donors said that the best aspects of the donation were helping another woman, being a medical pioneer, and the financial compensation. And this is a good lesson for recruiting donors for research purposes, Dr. Klock said. Egg donors often like to think of themselves as being in the medical world, as being a medical pioneer, and it is common for them to be involved in other medical programs—giving blood, for instance, or taking part in medical studies.

In particular, Dr. Klock said, reproductive donors are very interested in the outcome of their donation. They want to hear whether their donated eggs allowed a woman to give birth to a child. Dr. Klock said she believes that something similar will be true for women donating for research purposes. "If women are going to this kind of effort, they want to know that the reason that they were motivated to do this was met, whether that was a research goal or a reproductive goal."

Finally, the surveys showed that the donors who were motivated more by altruism and wanting to help others were more likely to be satisfied with their experience later on than were donors who were motivated mostly by the financial compensation. However, the role of financial compensation should not be dismissed. According to Dr. Klock, altruism and compensation often go hand in hand. Furthermore, in one study conducted 3 to 18 months post-donation, only 11 percent of participants reported that they would donate again if no compensation was provided.

Another study, three years post-donation, found that approximately half of the donors were motivated by financial reasons.

These surveys offer a number of lessons, Dr. Klock said. Overall, from 44 to 79 percent of the donors were satisfied with the experience. And a third of the donors were satisfied enough to complete more than one donation cycle.

Such repeat donors are very important to recruiters and IVF programs. Because the screening process is so labor-intensive, it saves a great deal of time and effort to have women who donate again and again, and this will be just as true for research donors as for reproductive donors. It is difficult, however, to know how the factors that lead women to donate multiple times for reproductive purposes will play when the donations are for research instead. When the purpose is reproduction, for example, some women may feel their need to help another woman is met after donating once; in the case of research programs, this same sort of thinking may not come into play. Another factor that may keep women from donating multiple times to a reproductive program is the fear of multiple offspring. If she donates eggs to multiple women, the possibility exists of having two or more biological offspring who were not aware that they are siblings, opening the door to the possibility of inadvertent incest. This would obviously not be a concern for research donors.

In contrast to the majority of women who are satisfied with the donation process, a minority of donors report having had a negative emotional reaction or regretting their decision to donate. "I see this as a failure in the screening process," Dr. Klock said. "We are not doing a good enough job in screening out donors who are ambivalent." In response, she said, she and colleagues are working on a project to modify a kidney donor ambivalence scale to see if it can be used to uncover some of the ambivalence that egg donors may feel. Another way to filter out more of these ambivalent donors, she said, would be to have a greater time lag between the time a donor is accepted into a program and the time that she undergoes the donation cycle. "I think just a little bit of time can allow a woman to fully think about the implications of what she may opt to do."

One other fact came to light from the surveys that is of particular interest to those looking to recruit women as research donors: 25 percent of the reproductive donors questioned said they would not want their eggs used to create research embryos. So it seems clear that not all of the women who donate their eggs for reproductive purposes would be willing to donate them for research. By the same token, there may well be

women who would not donate their eggs for reproduction but who would donate for research.

In conclusion, Dr. Klock said, the main negative psychological effects on egg donors after their donation were the regret and worry that were present for a minority of donors. The regrets can best be dealt with through a better selection process, which keeps out those who are ambivalent about the donation and thus likely to feel regrets later on, while the worries are best dealt with by communication and further research. Research is also necessary to counter the limitations of the studies discussed today, which include small sample sizes, single center, and cross-sectional design. Multicenter, longitudinal studies are needed in this area. "It is incumbent on us," she said, "to have meetings like this to review what the potential risks are and then communicate them to the women to the extent that we know them at the time. We need to continue to study and follow up on women who have gone through donation cycles to know what the potential risks are and how to counsel them appropriately."

SUMMARY: WHAT WE KNOW ABOUT THE PSYCHOLOGICAL RISKS OF OOCYTE DONATION

There are three main categories of psychological risk associated with donating eggs: issues associated with the screening process, problems surrounding the donation procedure itself, and the post-donation adjustment to the donation.

The main risk in the first category is that the screening process may reveal some previously unknown psychological or medical condition that disqualifies the woman from donating and that is uncomfortable or psychologically threatening to the applicant.

During the donation process, women report mood swings and irritability caused by the fertility drugs, pain caused by their injection, and anxiety in anticipation of the surgical procedure. The issues disappear after the procedure is complete.

After the eggs have been donated, the main psychological issues that donors experience are related to worries about future fertility and concerns about children conceived from their eggs. The latter will clearly not

be an issue with research donors. As for the former, the best response would be to have more and better research done on the issue of the risks of oocyte donation, so that these risks can be reported to the donors and they can be clear about what they are getting themselves into.

5

Directions for the Future

Much of the workshop was devoted to the question of what is known about the potential risks of oocyte donation. Those discussions were generally carried out with an eye to two other questions: What is still not known about the potential risks of oocyte donation (and how can one learn what one needs to know)? And how can the potential risks of oocyte donation best be minimized?

This chapter describes the discussions that centered on the latter two questions.

THE NEED FOR MORE AND BETTER DATA

One of the most striking facts about in vitro fertilization (IVF), Dr. Giudice commented, is just how little is known for sure about the long-term health outcomes for the women—and men—who undergo the procedures. Although more than a million IVF cycles have been performed in the United States over the past 20 years, and although there are registries that keep track of the various reproductive outcomes, such as the number of eggs retrieved and the number of children born, there are no registries that track the health of the people who have taken part. Without such registries to draw from, most of the studies of the health outcomes of IVF have been anecdotal or have focused on relatively small groups of people. Furthermore, Dr. Giudice noted, the studies vary quite a lot in terms of study design, the number of subjects, and outcome, so it is impossible to draw a consistent picture from them.

The situation is complicated by the fact that the available studies are not directly applicable to the question at hand—the safety of oocyte do-

nation for research. For one thing, Dr. Giudice pointed out, the available data come primarily from IVF patients and not from healthy subjects, yet it is healthy women and not those coping with infertility who will be donating eggs for research. This raises the possibility, for example, that the existing data will overstate the potential risks for healthy donors, given that IVF patients may be more likely to have a variety of conditions, such as pelvic adhesions and polycystic ovary syndrome, that increase the odds of complications from the ovarian stimulation or the retrieval surgery.

In addition, the available data come primarily from Caucasian women in middle to upper socioeconomic groups, because they are the women most likely to be able to pay for IVF on their own. Since fertility treatment is generally not covered, or not covered fully, by medical insurance, women in lower economic brackets are less often able to afford such treatments and so make up a relatively small percentage of women in IVF programs. But the pool of research donors is likely to be significantly broader than just Caucasian women in middle to upper socioeconomic groups, and it is difficult to infer just what potential risks these research donors may face when the only available data are from a collection of women who differ from them in age, race, and socioeconomic status.

One other complicating factor is that the potential risks from hormone therapy, from surgery, and from anesthesia seem to have been changing over the past 20 years. "Many of these risks," Dr. Giudice said, "seem to have been greater early in the process of in vitro fertilization than they are currently." The reason would seem to lie in the increasing experience that reproductive specialists have been accumulating, she said. By doing procedures over and over again, doctors hone their skills and learn to avoid certain mistakes, leading to a decline in potential risk. This decline is good news, of course, but it adds to the uncertainty about exactly what potential risks egg donors face now.

The bottom line is that there is a great deal of uncertainty about the potential risks of oocyte donation for research. David Guzick, dean of the University of Rochester School of Medicine and Dentistry, made this point when discussing the future fertility of egg donors:

"What we know about future fertility in connection with oocyte donation is really only by inference," he said. "What were presented [at the workshop] were data on general IVF patients and a much smaller amount of data on donors. We learned that the incidence of infection, the incidence of adhesions, and the incidence of general surgical problems is

low. We inferred from that, therefore, that the likelihood that there should be problems with fertility is low, but we don't really know that. We don't really have data to tell us, if these individuals who donated their eggs were followed, how their fertility would compare with a matched control group.

"We also know a lot about the biology of follicle selection," he continued, "and we know about the physiology of administering exogenous gonadotropins and the fact that, in repeated stimulation cycles, there does not appear to be a reduction in the number of eggs that are produced. And we might infer from that, therefore, that fertility may not be compromised in the future, but we don't really know that. We don't have data on individuals—healthy research subjects—who have undergone repeated stimulation cycles, and we don't have any data on what the future fertility of these individuals might be."

Similarly, he said, based on what is known about the biology of follicles over time, we do not think that even repeated donations will cause a woman to have an earlier menopause, but again there are no data that tell us that for sure. We don't really know that.

The only way to completely resolve these issues, Dr. Guzick said, is to follow a cohort of oocyte donors and observe what happens to them over time—to monitor their fertility over the years and compare it with a control population that did not donate their eggs. "And I think until we know that, we won't truly be reassured about future fertility," he said.

More generally, Dr. Giudice said, it is important to accumulate health data over the years for all women whose eggs are harvested for various purposes and to monitor them for long-term effects. "Almost every speaker addressed the issue of some type of database," she observed.

With more data—and more complete data—it will be possible to quantify the various potential risks of oocyte donation much better than can be done today and therefore to put numbers to the various potential risks that a potential donor faces. Doctors and medical researchers should be able to offer concrete answers to some questions: Does ovarian stimulation increase a woman's lifetime risk of uterine cancer? What effect does a history of pelvic inflammatory disease have on a woman's risk factors for retrieval surgery? A more complete database will also allow researchers to tease out the answers to other questions: What effect does having had children have on the risks of oocyte donation? Is there any reason to prefer one age range over another among women who are donating oocytes for research purposes? These are the sorts of questions

that are impossible to answer well without a great deal of data accumulated in a very deliberate and consistent way.

MINIMIZING POTENTIAL RISKS

Nearly all of the speakers cautioned against relying on probabilities because the most important strategy in collecting oocytes for stem cell research is to be cautious in relying on probabilities, because the most important strategy to minimize the potential risks to oocyte donors is to make decisions based on common sense on a case-by-case basis. Of course, physicians try not to subject any of their patients to unnecessary risks, but because research donors represent a special situation—women who are undergoing a procedure not for their own benefit but for the benefit of others—the workshop participants said that even greater care should be taken to make sure that these donors do not pay for their altruism with their own health.

"We absolutely want to minimize risk for our reproductive donors," said Dr. Marcelle Cedars. "For example," she said, "there might be risks in terms of a difficult position of an ovary or getting every last follicle that I might take for a patient that I wouldn't take for a reproductive donor. And perhaps we should go even one step beyond that in terms of our donors for research."

There was some discussion as to just how far to go to minimize potential risks, particularly with regard to the issue of excluding particular donors with certain risk factors. "I notice that we've all agreed we should be conservative," said Kurt Barnhart, director of the Center for Clinical Research on Women's Health at the University of Pennsylvania, "but we've all danced around the issue by not offering specifics on what should be excluded and what shouldn't." The issue, he said, is finding a balance—to minimize potential risk but "not exclude everybody who might want to participate. We need to be cautious, of course, to minimize potential risk, but we don't want to eliminate something without evidence for eliminating it."

Zev Rosenwaks had a somewhat different take. "The big difference between research donors and IVF patients," he said, "is that whenever possible, if you identify any irregularity, whether it be infectious, anatomic, or otherwise, a research donor should be excluded. We have to be careful to think about statistics, but at the end of the day common sense in terms of potential complications should rule."

Wherever the bar is set, everyone agreed that a great deal of effort should be taken to minimize potential risk for women who are donating their eggs for research. Therefore, much discussion at the workshop was devoted to how such potential risk can best be minimized.

There are two basic ways to minimize potential risk to egg donors. The first is to identify which potential donors have particular risk factors and to exclude them from the donor pool, since they have a higher than normal risk for complications. This is exactly how Cornell handles its egg donors, Dr. Rosenwaks said. "We eliminate patients with endometriosis, a history of PID [pelvic inflammatory disease], previous pelvic surgery, irregular menstrual bleeding, PCOS [polycystic ovarian syndrome], uterine myomas, familial thrombophilia, ovarian tumors, and any other medical condition that we feel may be a problem in terms of the stimulation. We feel that with stem cell research, we should have exactly the same criteria. We're not dealing with IVF patients. We're dealing with patients that are donating either altruistically or maybe for minimum pay. But at the end of the day, it is our responsibility to make sure that safety is paramount."

In determining which potential donors to accept and which to exclude, Dr. Giudice said, the importance of a thorough medical history cannot be overstated. "It's not enough just to ask about menstrual cycles," she said. "You really need to nail down how regular they are." And even things that might seem unrelated to oocyte donation—such as a pituitary tumor—can end up playing an important role. There have been rare cases, Dr. Giudice said, in which a woman with a pituitary tumor took gonadotropin-releasing hormone (GnRH) agonists as part of the hormone therapy and, as a result, suffered pituitary apoplexy.

Besides getting a thorough medical history, Dr. Giudice said, doctors should also use their diagnostic tools to identify potential risk factors. Ultrasound is particularly useful, she said, "in terms of assessing the pelvis for uterine fibroids, for possible endometriomas, for possible ovarian tumors, and also for the occasional malplaced ovary that may be in a place that may put the patient at risk for some of the surgical risks that Dr. Murphy discussed."

Another potential way to screen research donors, Dr. Giudice said, is by age. "What is the optimal age group? Is it the reproductive age span, 18 to 50? Is it the ovum donor population currently used for reproduction, 21 to 34? This is something that we just don't have any information on, but I think we are obliged to define that at some point for the safety of our donors."

Finally, she said, it is possible that the exploding growth of knowledge in genetics and genomics could eventually help doctors pinpoint which women will be at greatest or the least risk from oocyte donation. "My hope is that over the next ten years we'll have some information that will give us a bit more wisdom in terms of choosing our donors, not only for egg donation, but for other clinical trials as well."

The downside of being careful to exclude any potential donors that may be at higher risk from the procedure is that it greatly reduces the donor pool, Dr. Rosenwaks noted. At Cornell, for example, potential donors are screened in a wide variety of areas: "The donors see the psychologist, they see a genetic counselor, they see the physician, they go through a multiphasic personality test, and so on and so forth." The result is that over an 8-year period, of the 1,600 potential donors at Cornell who returned their questionnaires—and not counting the women who had called but never returned the questionnaires—only about 200 patients actually came in to donate. Only one out of eight women who had been interested enough to contact the program, get a questionnaire, fill it out, and return it actually ended up donating eggs.

This exclusionary approach can be applied to lessen any of the major potential risks from oocyte donation. In the case of potential surgical risks, for example, there are several factors that put women at higher risk from retrieval surgery, Dr. Murphy said. "I would not use someone who's at risk for complications, such as those with endometriosis and their increased risk of adhesions and endometriomas, nor would I probably use those that have had previous infectious disease."

Anesthesia, Dr. Barnhart said, has "the most identifiable and quantifiable differences" in risk thanks to the ASA (American Society of Anesthesiologists) classification. Only donors in the lowest risk category for anesthetic risk should be allowed to go through the retrieval surgery.

It should also be possible to screen women on the basis of risks to future fertility, said Dr. Nicholas Cataldo. One approach would be to look to older women who are sure that they have completed their families. But, he noted, it would be important to examine the relationship between donor age and research outcomes. For example, does a 32-year-old egg work as well for somatic cell nuclear transfer as a 22-year-old egg? It would also make sense to screen women for factors, such as a history of pelvic inflammatory disease or endometriosis, that would put them at a higher risk for fertility problems exacerbated by the retrieval surgery.

The second major approach to minimizing the potential risk of oocyte donation focuses on the process itself and asks what modifications

can be made to that process to make it less risky for the women who take part. This approach is particularly useful when it is done on a patient-by-patient basis, modifying the different procedures to take into account the particular medical characteristics of a donor. In theory, this technique can be applied to any of the potential risks of oocyte donation, but the workshop participants focused on its application to one potential risk in particular: the development of ovarian hyperstimulation syndrome caused by hormones used to stimulate the ovaries to produce more eggs.

PREVENTING OVARIAN HYPERSTIMULATION SYNDROME

Of all the risks facing women undergoing in vitro fertilization, the most common and the most threatening is ovarian hyperstimulation syndrome (OHSS). As described in Chapter 2, studies have found that a large percentage of women undergoing ovarian stimulation experience symptoms of OHSS ranging from mild to severe, and thus women donating their eggs for research could be expected to face similar complications.

According to several of the speakers at the workshop, it should be possible to prevent many cases of OHSS, including all or almost all of the most severe cases. That prevention will require a combination of the two basic risk minimization strategies: identifying and excluding from treatment those women most at risk and, for those women who do undergo ovarian stimulation, modifying the treatment according to the characteristics of the individual patient.

For some women, Dr. Cedars said, the risk of OHSS is just too great to allow them to be research donors. “I would recommend exclusion of women with polycystic ovarian syndrome,” she said, “because I believe their response, even with careful monitoring, is quite difficult to predict and control.” She would also exclude women who don’t have full-blown PCOS but who have polycystic-like ovaries according to the ultrasound pictures and also women with irregular menstrual cycles. Some doctors, she noted, would even exclude women if they have elevated levels of androgens of luteinizing hormone, but she is comfortable leaving these in the pool if they are otherwise asymptomatic and have a normal-appearing ovary on ultrasound.

Dr. Rosenwaks said he follows a similar protocol in his center. As donors, he excludes not only women with the classic polycystic ovarian

syndrome but also patients who exhibit polycystic ovaries on ultrasound but no biochemical changes—normal follicle-stimulating hormone and luteinizing hormone and normal menstrual cycles.

With the most highly at-risk women excluded, Dr. Cedars said, the second step is to tailor the stimulation protocol to the individual donors with the goal of avoiding ovarian hyperstimulation in each. So it is important to understand just what it is that triggers OHSS.

As Dr. Rosenwaks explained, the development of ovarian hyperstimulation syndrome depends on a large number of follicles in the ovary being exposed to human chorionic gonadotropin (hCG), which is used as a surrogate for luteinizing hormone in order to induce the follicles to ovulate. So there are at least two approaches that can be taken to avoid OHSS: controlling the number of follicles that develop in the ovary and modifying their exposure to hCG.

"For a young fertile donor who might have 20-plus follicles," Dr. Cedars said, "you really don't want all 20 of those follicles. I think what you shoot for is maybe 10 to 15." To do this, she explained, the doctor uses ultrasound to examine the ovary and count the number of antral follicles before the start of the hormone treatment. The doctor then uses this information along with the patient's age and weight to determine a starting dose.

"The main factor that goes into determining this initial start dose," she said, "is the antral follicle count, because, remember, with the most aggressive stimulation we're going to get plus or minus two of that number. So if we have a patient with very high number of antral follicles, we don't want all those follicles to develop. We're going to decrease the dose." Over the course of the treatment, the physician continues to monitor the patient's progress and will further decrease the dose if too many follicles are developing or if the estradiol levels are too high.

And if for some reason, after a week and a half of hormone treatment, too many follicles have developed, OHSS can still be controlled by manipulating the dose of hCG used to induce ovulation, Dr. Cedars said. "If you don't give hCG, you will not get hyperstimulation."

At Cornell, Dr. Rosenwaks said, of 841 egg donor cycles started over the 14-year period from 1992 through 2005, 20 were canceled because of the risk of hyperstimulation at the stage at which hCG would normally have been applied. "We did not take them to retrieval." Instead the eggs were consigned to atresia, the reabsorption back into the body. "You withhold hCG, you do not get hyperstimulation," he said, echoing Dr. Cedars. And, indeed, of the 800-plus egg donor cycles at Cornell from

1992 through 2005, there was not a single case of severe OHSS, Dr. Rosenwaks said.

There are other ways to modify the hCG ovulation trigger without completely cutting it out, Dr. Cedars said. "One is to decrease the dose of hCG, because part of the reason that you get that hyperstimulation three to seven days after the injection of hCG is because of the long half-life of hCG. So if you decrease the initial dose, you decrease the time in which hCG levels are circulating and high enough to cause the continued stimulation to the ovary, and there's some evidence to suggest you can decrease the occurrence of hyperstimulation."

It is also possible, she noted, to use recombinant LH, which has the same effect as hCG of inducing ovulation, but it has a shorter half-life and thus does not stay in the body as long. There is some preliminary evidence suggesting that this technique decreases the occurrence and the duration of ovarian hyperstimulation.

As doctors and medical researchers learn more about the way that these hormones work in the body, more options will undoubtedly open up as well, but today we already have the capability of avoiding severe OHSS almost completely, Dr. Rosenwaks concluded. "With careful donor selection, individualization of stimulation protocols, careful monitoring, and utilizing appropriate preventive measures, severe OHSS can be virtually eliminated," he said.

ALTERNATIVE SOURCES FOR OOCYTES

Given that there is always going to be some potential risk to egg donation, it makes sense to look for alternate sources of eggs—sources that do not rely on the traditional process of ovary stimulation and surgical retrieval that was developed for in vitro fertilization. The workshop participants discussed several of these alternatives.

One possibility, as Dr. Guzick pointed out, is to take advantage of an existing resource—that is, couples who have undergone IVF and who may have embryos they don't wish to use themselves and which might be available for donation. At this point, no one really knows how many such embryos there are, but it should be worth looking into.

Catherine Racowsky, associate professor of obstetrics, gynecology, and reproductive biology at Harvard Medical School, brought up a second alternative. "In a typical IVF cycle," she said, "only about 80 percent of the eggs are mature. Of the remaining 20 percent, some of them are

completely immature, and some of them are partially mature." At this point, in a typical IVF labs, those immature and partially mature eggs are discarded, but researchers are working on ways to mature such eggs in vitro, so that they can be recovered and used. If these techniques can be perfected, this would be a way to increase the supply of eggs without the need for more donors.

On a related note, Dr. Cataldo pointed out that techniques are being developed to mature eggs in vitro after only a very brief exposure to hormones, primarily hCG. This could greatly increase the potential donor pool. For example, in women who have a number of small antral follicles, it might be possible to retrieve a significant number of oocytes without putting the woman through the usual ovarian stimulation. Clinical studies have already shown that these oocytes can be successfully fertilized after being matured in vitro, Dr. Cataldo said. So women who might otherwise be excluded from donating their eggs for research—such as women with polycystic-appearing ovaries—could in this way provide eggs without the potential risks that would accompany such a donation done via the usual path.

Finally, there was some discussion about the possibility of retrieving oocytes from cadavers in much the same way that organs are now retrieved from the bodies of people who have signed organ donation cards. As Dr. Giudice put it, in addition to donating your organs to science you might want to donate your gametes.

For that to become a reality, it would be necessary to be able to store oocytes from cadavers in such a way that they remain viable until they can be used. At this time, Dr. Racowsky said, medical researchers are working to perfect the technique of oocyte freezing. "Some programs are having really quite good success rates with egg freezing now," she said, "but it's not universally the case. With a little bit more experience and technological advances, hopefully in the near future we'll have that also as a useful tool to be able to store very valuable material for this work." If so, it should open up one more alternative source of oocytes.

For now and for at least the near future, however, the major source of oocytes for research is likely to remain eggs donated by women specifically for use in research.

A

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B

Public Workshop on Assessing the Medical Risks of Human Oocyte Donation for Stem Cell Research

Hyatt Regency San Francisco Airport
11333 Bayshore Highway
Burlingame, CA 94010

Thursday, September 28, 2006
The Regency Ballroom Salons B&C

8:00 a.m. **WELCOME AND INTRODUCTIONS**

Linda Giudice
Committee Chair
Professor and Chair, Department of Obstetrics, Gynecology and Reproductive Sciences
The Robert B. Jaffe, M.D. Endowed Chair in the Reproductive Sciences
University of California, San Francisco

Zach Hall
President
California Institute for Regenerative Medicine

8:15 a.m. **OVERVIEW AND HISTORICAL PERSPECTIVE**

Linda Giudice
Committee Chair
Professor and Chair, Department of Obstetrics, Gynecology and Reproductive Sciences
The Robert B. Jaffe, M.D. Endowed Chair in the Reproductive Sciences
University of California, San Francisco

Session I
Moderator: Joe Leigh Simpson

9:00 a.m. **OVARIAN HYPERSTIMULATION SYNDROME**

Marcelle Cedars
Director
Division of Reproductive Endocrinology and Infertility
University of California, San Francisco

9:30 a.m. **SURGICAL RISKS**

Ana Murphy
Brooks Professor and Chair
Department of Obstetrics and Gynecology
Medical College of Georgia

9:50 a.m. **ANESTHETIC RISKS**

Lawrence Tsen
Associate Professor in Anesthesia
Harvard Medical School
Director of Anesthesia
Center for Reproductive Medicine
Brigham and Women's Hospital

10:10 a.m. **PANEL DISCUSSION**

Panel will include all Session I speakers, plus *Kurt Thomas Barnhart* (Associate Professor, Department of Obstetrics and Gynecology and Epidemiology, and Director Center for Clinical Research on Women's Health, University of Pennsylvania), as an invited discussant.

10:45 a.m. **BREAK**

Session II
Moderator: Bernard Harlow

11:10 a.m. **PSYCHOLOGICAL RISKS**

Susan Klock
Professor
Departments of Obstetrics and Gynecology and Psychiatry
Northwestern University Medical School

11:35 a.m. **CANCER RISKS**

Roberta Ness
Professor and Chair
Department of Epidemiology
University of Pittsburgh

12:05 p.m. **PANEL DISCUSSION**

Panel will include all Session II speakers, plus *John Collins* (Professor Emeritus, Department of Obstetrics and Gynecology, McMaster University, Hamilton), as an invited discussant

12:30 p.m. **LUNCH**

Session III
Moderator: Catherine Racowsky

1:30 p.m. **FUTURE FERTILITY**

Nicholas Cataldo
Formerly Assistant Professor
Department of Obstetrics and Gynecology
Stanford University

2:00 p.m. **SIMILARITIES AND DIFFERENCES IN THE PROCESS OF OOCYTE DONATION FOR CLINICAL TREATMENT VERSUS RESEARCH**

Zev Rosenwaks
Director, Revlon Distinguished Professor of Reproductive Medicine
The Center for Reproductive Medicine and Infertility
Department of Obstetrics/Gynecology
Cornell University

2:30 p.m. **PANEL DISCUSSION**

Panel will include all Session III speakers, plus *David S. Guzick* (Dean, University of Rochester School of Medicine and Dentistry), as an invited discussant

3:00 p.m. **BREAK**

Session IV
Panel Discussion with All Speakers

3:15 p.m. **SYNTHESIS AND REVIEW: CURRENT KNOWLEDGE, GAPS, HOW TO AVOID RISKS, FUTURE CONSIDERATIONS**

Linda Giudice
Committee Chair
Professor and Chair, Department of Obstetrics, Gynecology and Reproductive Sciences
The Robert B. Jaffe, MD Endowed Chair in the Reproductive Sciences
University of California, San Francisco

4:15 p.m. **GENERAL DISCUSSION WITH AUDIENCE**

Linda Giudice
Committee Chair
Professor and Chair, Department of Obstetrics, Gynecology and Reproductive Sciences
The Robert B. Jaffe, MD Endowed Chair in the Reproductive Sciences
University of California, San Francisco

5:30 p.m. **ADJOURN**

C

Workshop Attendees

Lusine Aghejanova
University of California,
San Francisco

Shabbir Ahmad
California Department of Health
Services

Sarah Angel
Boalt Hall School of Law
University of California,
Berkeley

Denise Bernstein
University of California, San
Francisco

Dale Carlson
California Institute for
Regenerative Medicine

R. Alta Charo
University of California, Berkeley

Patricia Chavira
California Institute for
Regenerative Medicine

Erika Check
Nature

Arlene Chiu
California Institute for
Regenerative Medicine

L. Stephen Coles
University of California, Los
Angeles

Mary Croughan
University of California, San
Francisco

Susan Berke Fogel
Pro-Choice Alliance

David Grainger
University of Kansas

Carl Hall
San Francisco Chronicle

Zach Hall
California Institute for
Regenerative Medicine

Amy Hamilton
University of California, San Francisco

John Jain
University of Southern California

David Jensen
California Stem Cell Report

Aimee Kelley
University of California, Berkley

Ann Kiessling
Harvard Medical School

Sandy Kleffman
Contra Costa Times

Kirk Kleinschmidt
California Institute for Regenerative Medicine

Elizabeth Langdon-Gray
University of California, Office of the President, Office of Research

So Hyun Lee
University of California, San Francisco

Geoffrey Lomax
California Institute for Regenerative Medicine

Bertram Lubin
Children's Hospital Oakland Research Institute

Mary Maxon
California Institute for Regenerative Medicine

Juanito Meneses
University of California, San Francisco

Patricia Olson
California Institute for Regenerative Medicine

Joe Palca
National Public Radio

Richard Paulson
University of Southern California

Don Reed
Californians for Cures

Jesse Reynolds
Center for Genetics and Society

Gil Sambrano
California Institute for Regenerative Medicine

Gerald Schatten
University of Pittsburgh

Shehua Shen
University of California, San Francisco

Kate Shreve
California Institute for Regenerative Medicine

Joe Leigh Simpson
Baylor College of Medicine

Shannon Smith-Crowley
American Society for Reproductive Medicine

David Smotrich
La Jolla IVF

Susan Stayn
Partners Healthcare, Harvard

Jeff Stryker
Independent Writer
San Francisco, California

Charis Thompson
University of California, Berkeley

Terri Thorfinnson
California Department of Health Services

Sean Tipton
American Society for Reproductive Medicine

Nam Tran
University of California, San Francisco

Kim Chi Vo
University of California, San Francisco

Aubrey Wade
University of California, San Francisco

Richard Wagner
University of California, San Francisco

Zipora Weinbaum
California Department of Health Services

Adrianne Wong
Juvenile Diabetes Research Foundation

D

Glossary

adhesion — an abnormal band of tissue that can grow in the body, typically as a side effect of surgery, and cause two adjoining bodies to stick together

adult stem cell — a type of undifferentiated cell found in children and adults that has the ability to divide indefinitely and to generate all the different cell types found in the organ from which it comes; it has been suggested that adult stem cells could be used to regenerate organs

androgen — any of the various male sex hormones, including testosterone

antibody — a protein used by the immune system to fight infection by identifying and helping to neutralize the infecting agents, such as bacteria or viruses

antral follicle — a follicle in the final stage before ovulation

ascites — an accumulation of fluid in the abdomen between the abdominal wall and the internal organs, that is, in the peritoneal cavity

aseptic — sterile; free of germs

assisted reproductive technology (ART) — a medical treatment for infertility, such as in vitro fertilization

atresia — the process by which an immature follicle degenerates and is reabsorbed by the body

blastocyst — an early-stage embryo containing between 50 and 150 cells; its inner cell mass often serves as the source for embryonic stem cells

capnography — a technique for monitoring the levels of carbon dioxide being inhaled and exhaled, thus giving an indirect measure of blood carbon dioxide levels

clomiphene — a fertility drug that acts by inhibiting the action of estrogen on the pituitary gland, stimulating the gland to release more follicle-stimulating hormone

creatinine — a molecule formed in muscle tissue as a byproduct of the breakdown of creatine phosphate

desaturation — a lowering of the oxygen content of the blood

embryo — the product of a fertilized egg and its ongoing development from the time it implants itself in the uterus (at five to seven days after fertilization) until the eighth week of development, after which it is considered a fetus

embryonic stem cell — a stem cell that can give rise to any type of cell in the body; it is derived from the inner cell mass of a blastocyst, an embryo that is four to five days into development

endometrioma — a cyst in the ovary caused by the presence of endometrial tissue, that is, tissue similar to the lining of the uterus

endometriosis — a medical condition caused by tissue like that of the lining of the uterus (endometrium) being found elsewhere in the body; the symptoms include internal bleeding, inflammation, formation of scar tissue, and interference with the normal functioning of the surrounding tissue

estradiol — the major female sex hormone; it plays many roles, including serving as the trigger for the surge of luteinizing hormone that induces ovulation

estrogen — any of various female sex hormones, including estradiol

estrogen receptor — a protein on the surface of a cell or inside it that binds to an estrogen molecule and, in response to its presence, sets in motion various activities within the cell, such as the production of certain proteins

fallopian tube — a thin tube that carries eggs from the ovaries to the uterus

fertility drugs — generally speaking, any medication that increases fertility, but most often used to denote drugs that stimulate the development of follicles in the ovary

follicle — the roughly spherical structure in the ovary that contains the oocyte

follicle-stimulating hormone (FSH) — a hormone secreted by the pituitary gland that acts in the ovaries to stimulate the maturation of follicles

follicular sac — a fluid-filled portion of the follicle that contains the oocyte

gonadotropin — a general type of hormone secreted by the pituitary gland; specific types of gonadotropins include luteinizing hormone, follicle-stimulating hormone, and human chorionic gonadotropin

gonadotropin-releasing hormone (GnRH) — a hormone produced by the hypothalamus that triggers the release of luteinizing hormone and follicle-stimulating hormone from the pituitary gland

gonadotropin-releasing hormone agonist — a synthetic hormone designed to act on the same receptors that gonadotropin-releasing hormone acts on and thus to cause a similar effect

hemoconcentration — a decrease in blood volume that leads to an increased concentration of red blood cells

hormone — a substance that acts as chemical messenger in the body, being produced in one place and traveling through the bloodstream to trigger some action in another

human chorionic gonadotropin (hCG) — a hormone produced by the developing embryo to promote the development of the corpus luteum and, ultimately, to help prepare the lining of the uterus for the fetus; because of its chemical similarity to luteinizing hormone, it is often used during a course of ovarian stimulation to induce ovulation

hyperstimulation — *see* ovarian hyperstimulation syndrome

hypogastric artery — the main artery of the pelvis, supplying blood to the pelvic area, the buttocks, and the reproductive organs; also known as the internal iliac artery

in vitro fertilization (IVF) — a technique used in infertility treatments and in research by which an egg is fertilized outside the body

inhibin b — a hormone that inhibits the synthesis and secretion of follicle-stimulating hormone; it is thought to be released by a dominant follicle to cause the pituitary gland to produce less follicle-stimulating hormone and so cause competing follicles to stop growing

inner cell mass — the group of cells on the inside of a blastocyst that contains the embryonic stem cells

luteinizing hormone (LH) — a hormone produced by the pituitary gland that triggers ovulation when its levels spike

meta-analysis — a technique for combining the data and results from a number of different studies addressing the same or similar questions and using those combined studies to come to a conclusion that can be more trustworthy than the results of any single one of the individual studies

mittelschmerz — a lower abdominal or pelvic pain felt by some women midway through their menstrual cycle, or around the time of ovulation

myoma — a type of tumor, the most common of which is the uterine fibroid, which grows in the uterus

nociceptors —nerve endings in the skin, muscle, and internal organs that are responsible for the sensation of pain

oocyte — the female germ cell that, after it matures, can be fertilized by a sperm cell to create an embryo; an ovum or egg before maturation

ovarian hyperstimulation syndrome (OHSS) — a possible complication of ovarian stimulation; symptoms include increased ovarian size, nausea and vomiting, increased permeability of the blood vessels, leading to an accumulation of fluid in the abdomen, breathing difficulties, hemoconcentration, and, in the most severe cases, blood clots or kidney failure

ovarian stimulation — the use of fertility drugs to rescue eggs that would otherwise be lost in a monthly cycle and cause an elevated number of mature eggs to be available in the ovary

ovarian torsion — a situation in which the ovary twists around on itself, cutting off its blood supply

ovulation — the rupture of a mature follicle and release of its egg

paracervical block — a type of anesthesia sometimes used during childbirth that involves injecting a local anesthetic on either side of the cervix

pelvic abscess — a collection of pus that forms in a cavity in the pelvic region in response to infection or the presence of a foreign object

pelvic inflammatory disease (PID) — an inflammation of the female reproductive tract, including the uterus, fallopian tubes, and ovaries, caused by an infection and whose symptoms can include fever, ab-

dominal pain, and abnormal discharge; it is the leading cause of sterility among women

perineum — in females, the surface region between the pubic bones and the coccyx (tailbone), containing the vagina and the anus

peritoneum — the membrane that lines the abdominal cavity

peritonitis — an inflammation of the peritoneum

pituitary apoplexy — a bleeding within the pituitary gland that can cause headache, confusion, and loss of consciousness

pituitary gland — a gland at the base of the brain that secretes hormones that are involved in regulating a number of body functions, including growth, blood pressure, and the production of eggs

polycystic ovarian syndrome (PCOS) — an endocrine disorder characterized by multiple cysts in the ovaries, irregular or missing ovulation, and a higher-than-usual level of androgens

primordial follicle — a follicle that has not begun development toward a mature follicle

progesterone — a hormone that plays a number of roles in the menstrual cycle and pregnancy

pulse oximetry — a technique for measuring the oxygenation of blood by passing infrared light through a finger, ear lobe, or other thin part of the anatomy

somatic cell nuclear transfer — the process of taking the nucleus from a somatic cell (a cell other than a sperm or an egg cell) and putting it into an egg in place of the egg's own nucleus; since a cell's DNA is contained in its nucleus, an egg produced by somatic cell nuclear transfer has the genetic material from the donor of the somatic cell; the technique is used in stem cell research to create stem cells that are genetically identical to the donor

stem cell — a primal cell that can divide indefinitely and that can differentiate into a number of different types of cells

stem cell therapy — the use of stem cells to treat disease or injury; medical researchers believe that stem-cell-based treatments have the potential to treat a large number of diseases, including chronic heart disease, Type I diabetes, and Parkinson's disease, as well as many types of injuries, such as spinal cord damage, the brain damage caused by a stroke, and the damage to heart muscles caused by a heart attack.

tamponade — an absorbent dressing used to stop bleeding

thrombophilia — an increased tendency to develop blood clots

torsion — *see* ovarian torsion

transvaginal probe — an instrument used to retrieve eggs from the ovary

ureter — one of the ducts that carry urine from the kidneys to the bladder

E

Biographical Sketches of Committee Members, Invited Speakers, and Staff

COMMITTEE MEMBERS

Linda C. Giudice, M.D., Ph.D., M.Sc. (*Chair*), is professor and chair of the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of California, San Francisco, where she holds the Robert B. Jaffe, M.D., endowed chair in the reproductive sciences. She received her Ph.D. in biochemistry from the University of California, Los Angeles, and an M.D. from Stanford University, after postdoctoral training at Rockefeller University and the National Institutes of Health. Dr. Giudice completed her residency in obstetrics and gynecology at Stanford University and Washington University in St. Louis and was a fellow in reproductive endocrinology and infertility at Stanford. In 1987, she joined the faculty of the Stanford University School of Medicine and in 2005 was named the Stanley McCormick memorial professor emerita. While at Stanford, Dr. Giudice served as founding director of the Center for Research on Reproduction, Women's Health and Genomic Medicine and was director of the Reproductive Endocrinology and Infertility Division from 1994 to 2005. Dr. Giudice was elected to the Institute of Medicine in 2002 and has been affiliated with the Institute for Stem Cell and Tissue Biology at the University of California, San Francisco, since 2005, where she serves on the Gamete, Embryo, and Stem Cell Research Oversight Committee, the Stem Cell Research Coordinating Committee, and the Stem Cell Research Program Committee. She has a major interest in human embryonic stem cells and somatic cell nuclear transfer from the perspective of policy and human subject protection. Her research focuses on disorders of the endometrium leading to infertility and pregnancy disorders and translating findings to diagnostics and therapeutics for women

with infertility and endometriosis and related disorders. Clinically, her focus is on patients needing assisted reproduction, as well as ovulatory dysfunction and endometriosis.

Ezra C. Davidson, Jr., M.D., is associate dean of primary care and professor in the Department of Obstetrics and Gynecology at the Charles R. Drew University of Medicine and Science. He currently is also a professor in obstetrics and gynecology at the David Geffen School of Medicine of the University of California, Los Angeles. He was chief of service in the Department of Obstetrics and Gynecology at the King/Drew Medical Center in Los Angeles from 1991 to 1996. Dr. Davidson is currently president of the Association of Academic Minority Physicians and a member of the Board of Governors of the Jacobs Institute of Women's Health. Dr. Davidson has a major interest in maternal and child health and has had many roles in public policy related to women's reproductive health and infant health. He is currently a member of the American College of Obstetricians and Gynecologists' National Fetal and Infant Mortality Review Program and of the California State Department of Health Services' Black Infant Health Leadership Committee. He chaired the federal health and human services secretary's Advisory Committee on Infant Mortality from 1991 to 1995 and served as president of the American College of Obstetricians and Gynecologists from 1990 to 1991. He received his B.S. in zoology from Morehouse College and his M.D. from Meharry Medical College. He is a member of the Institute of Medicine and has been involved in a number of study committees on issues of national health policy. He cochaired the Committee on Perinatal Transmission of HIV and served as a member of the IOM Committee on the Impact of Pregnancy Weight on Maternal and Child Health.

Naihua Duan, Ph.D., is professor in residence in the departments of Psychiatry and Biobehavioral Science and Biostatistics and the Jane and Terry Semel Institute for Neuroscience and Human Behavior at the University of California, Los Angeles (UCLA). He is also director of methods core at the UCLA/RAND Center for Research on Quality in Managed Care. He has been involved in health services research for more than 20 years, working on innovative design paradigms for clinical and public health research. Dr. Duan was corporate chair and senior RAND fellow in statistics from 1979 to 2000. He currently serves as member of the Editorial Board for Health Services and Outcomes Research Methodology, the Scientific Advisory Board of the Prevention

Center for Families in Stress at Arizona State University, and the National Institute of Mental Health's Review Committee on Mental Health Services in Mental Health Specialty Settings. He served on the Advisory Committee for the 2005 International Conference on Health Policy Research, and as director of methods core for the Center for HIV Identification, Prevention, and Treatment Services at the Charles R. Drew University, RAND, and UCLA. He received his B.S. in mathematics from National Taiwan University and his Ph.D. in statistics from Stanford University. Dr. Duan has also served as a member of the National Academies/Institute of Medicine's Committees on Organ Procurement and Transplantation Policy, Advances on Assessing Human Exposure to Airborne Pollutants, and Carbon Monoxide Episodes in Meteorological and Topographical Problem Areas.

Bernard L. Harlow, Ph.D., is a Mayo professor of public health and the division head of epidemiology and community health at the University of Minnesota. He is also an adjunct professor of epidemiology at the Harvard School of Public Health. Previously, he was assistant professor (1989-1996) and associate professor (1996-2005) of obstetrics, gynecology and reproductive biology at Harvard Medical School, and associate professor in the Department of Epidemiology at the Harvard School of Public Health from 1999 to 2005. He was also the co-director of the Obstetrics and Gynecology Epidemiology Center at Brigham and Women's Hospital from 1990 to 2005. Dr. Harlow has published extensively in the area of women's reproductive and mental health. Currently, he is a member of the National Institutes of Health–Center for Scientific Review's Reproductive Epidemiology Study Section and the Advisory Board of the Center of Excellence in Women's Health at the University of Minnesota, and he has served on a number of federally sponsored special emphasis panels on reproductive health research. Dr. Harlow is on the Editorial Board of the *American Journal of Epidemiology* and has reviewed manuscripts for many top-tier medical journals, including *Fertility and Sterility*, the *American Journal of Obstetrics and Gynecology*, and the *New England Journal of Medicine*. He received his B.S. from the University of Rhode Island, his M.P.H. in epidemiology from the University of Minnesota, and his Ph.D. in epidemiology from the University of Washington.

Susan C. Klock, Ph.D., is professor in the Department of Obstetrics and Gynecology and the Department of Psychiatry at Northwestern University as well as a clinical psychologist at Northwestern Memorial Hospital. She was director of the Women's Mental Health Service from 1992 to 1994 and associate clinical psychologist in medicine from 1991 to 1994, both at Brigham and Women's Hospital. She was also assistant professor at the Department of Obstetrics and Gynecology and Psychiatry at the University of Connecticut Medical School from 1989 to 1991 and instructor in the Division of Psychiatry, Department of Medicine, at Harvard Medical School from 1991 to 1994. Dr. Klock has been involved in multiple activities related to the psychological aspects of infertility and ovum donation. Currently, she serves as chair of the Regulation Task Force of the Mental Health Professional Group for the American Society for Reproductive Medicine (ASRM) and of the Credentialing Committee for the International Infertility Counseling Organization. She was member of the Oocyte Donation Task Force, Psychological Interest Group of ASRM from 1991 to 1993, and a member of the Embryo Donation Task Force of National RESOLVE from 2002 to 2004. Her research addresses the mental health aspects of infertility, in vitro fertilization, and ovum donation. She received her B.A. in psychology and computer science from Butler University and her Ph.D. in clinical psychology from Bowling Green State University.

Judith LaRosa, PhD, RN, FAAN, is deputy director of the Masters of Public Health Program and professor in the Department of Preventive Medicine and Community Health at the State University of New York, Downstate Medical Center. She served as professor and chair of community health sciences at the Tulane University School of Public Health and Tropical Medicine from 1996 to 1999. Dr. LaRosa has extensive experience in public policy on women's health. She was director of the Tulane Xavier National Center of Excellence in Women's Health from 1998 to 1999, associate project director at the National Science Foundation's Louisiana Project from 1994 to 1999, and deputy director of the Office of Research on Women's Health at the National Institutes of Health. She is also a journal reviewer for various public health and women's health publications, including the *American Journal of Public Health*, the *American Journal of Preventive Medicine*, the *Journal of the American Medical Women's Association*, and the *Journal of Women's Health*. She received her B.S. in nursing and M.N.Ed. from the University of Pittsburgh and her Ph.D. in health education from the University of Mary-

land. She has served as a member of the Institute of Medicine's Committees on Understanding the Biology of Sex and Gender Differences and Defense Women's Health Research.

Catherine Racowsky, Ph.D., HCLD, is associate professor of obstetrics, gynecology and reproductive biology at Harvard Medical School and director of the Assisted Reproductive Technology Laboratory at Brigham and Women's Hospital. She was associate professor at the University of Arizona from 1991 to 1997 and director of the Assisted Reproductive Technology Laboratory at the University of Arizona Medical Center from 1991 to 1997. Dr. Racowsky is currently a member of the Assisted Reproductive Technology Ethics Committee, the Center for Reproductive Medicine Leadership Committee, and the Partners' Embryonic Stem Cell Research Oversight, all at Brigham and Women's Hospital. She also serves as president of the New England Fertility Society and as a member of the Practice Committee of the American Society for Reproductive Medicine and the International Stem Cell Guidelines Task Force of the International Society for Stem Cell Research. In addition to her extensive clinical experience with assisted reproductive technology, she has an extensive publication record on oocyte maturation and embryo development and has been involved in other activities in this field throughout her career. Previously, she was a member of the Executive Council of the Society for Assisted Reproduction Technology (2004-2006) and member of the Editorial Board of *Reproductive Toxicology* (1997-2001) and *Human Fertility* (2004-2006). She received her B.A. from the University of Oxford and her Ph.D. in reproductive physiology from the University of Cambridge, England. She was a Lalor Foundation fellow in reproduction from 1976 to 1977 and a Research fellow in reproduction from 1976 to 1977, both at Harvard Medical School. Dr. Racowsky participated as a discussant at the Institute of Medicine's Workshop on Guidelines for Human Embyonic Stem Cell Research.

Zev Rosenwaks, M.D., is the Revlon distinguished professor of reproductive medicine in obstetrics and gynecology and professor of reproductive medicine in the Cornell Institute for Reproductive Medicine, both at Weill Medical College of Cornell University. He is the director and physician-in-chief of the Center for Reproductive Medicine and Infertility and attending obstetrician-gynecologist, all at New York Presbyterian Hospital–Weill Cornell. He is an internationally recognized authority on reproductive endocrinology and infertility with an extensive

publication record in this area. He is also a founding pioneer of assisted reproductive technologies. Dr. Rosenwaks is a diplomate and fellow of the American Board of Obstetrics and Gynecology. He has also been involved in many national and international activities related to assisted reproductive technology (ART) and in vitro fertilization (IVF). Dr. Rosenwaks was president of the Society for Reproductive Endocrinologists from 1987 to 1988, president of the Society for Assisted Reproductive Technologies from 1991 to 1992 and a member of the International Advisory Committee for the Sixth World Congress on IVF and ART in 1987 and for the Ninth World Congress in 1995. He is currently a member of the Editorial Board for *Assisted Reproduction News* and *Seminars in Reproductive Endocrinology*, and editor of the *Journal of Assisted Reproductive Technology/Andrology* (ARTA). Dr. Rosenwaks was also a member of the Editorial Advisory Board of the Weill Medical College Encyclopedia of Health and Healing. He received his B.A. in biology from the City University of New York and his M.D. from the State University of New York–Downstate Medical Center.

Joe L. Simpson, M.D., is professor of obstetrics and gynecology and professor of molecular and human genetics at Baylor College of Medicine. From 1994 to 2006 he was Ernst W. Bertner chairman of the Department of Obstetrics and Gynecology at Baylor. From 1986 to 1994 he was faculty professor and chairman of the Department of Obstetrics and Gynecology at the University of Tennessee. Prior to that he was head of the Section of Human Genetics and professor of obstetrics and gynecology, both at Northwestern University Medical School. Dr. Simpson is a leading researcher in the field of reproductive genetics, specifically in prenatal genetic diagnosis, preimplantation genetic diagnosis, and the genetics of gynecologic disorders, including premature ovarian failure. He has written a dozen major books, and approximately 650 chapters and peer-reviewed articles. He has served on over a dozen editorial boards, including the *American Journal of Medical Genetics*, *Prenatal Diagnosis*, *Reproductive Biomedicine Online*, the *Journal of the Society for Gynecologic Investigation*, and *Human Reproduction Update*. He was president of the American Society of Reproductive Medicine (ASRM) from 1993 to 1994 and president of the Society for Gynecologic Investigation (SGI) from 1998 to 1999. He is currently president of the Preimplantation Genetic Diagnosis International Society (PGDIS) and president-elect of the American College of Medical Genetics (ACMG). He is a current member of the Board of Scientific Counselors of the Na-

tional Institute of Child Health and Human Development and previously served on its Advisory Council. He is on the March of Dimes Scientific Advisory Committee. Dr. Simpson majored in chemistry at Duke University and received his M.D. from the Duke University Medical School in 1968. Postgraduate training in pediatrics (internship), obstetrics and gynecology (residency) and genetics was taken at Cornell Medical School–New York Hospital. He has been a member of the Institute of Medicine since 1994, serving on the Maternal and Child Health and Human Development Committee and the Committee on Improving Birth Outcomes in Developing Countries.

INVITED SPEAKERS

Kurt T. Barnhart, M.D., M.S.C.E., is the director of the Center for Clinical Research in Women's Health, associate director of the Division of Reproductive Endocrinology and Infertility, and associate professor in both the Department of Obstetrics and Gynecology and the Department of Epidemiology, all at the University of Pennsylvania. He received his medical degree from Mount Sinai School of Medicine and his M.S.C.E. degree (clinical epidemiology and biostatistics) from the University of Pennsylvania. He is board certified in obstetrics and gynecology as well as reproductive endocrinology and infertility. Dr. Barnhart is currently on the Executive Board of the Society of Reproductive Endocrinology and Infertility (SREI) and the Association of Reproductive Health Care Professionals (ARHP). He is also on the Editorial Board for the journals *Fertility and Sterility* and *Menopausal Medicine*. His research efforts regarding reproduction, family planning, early pregnancy, and menopause have been published in such journals as the *New England Journal of Medicine,* the *Annals of Internal Medicine,* the *Journal of Clinical Endocrinology and Metabolism,* the *Journal of the American Medical Association, Fertility and Sterility,* and *Human Reproduction*.

Nicholas Cataldo, M.D., is a former assistant professor in the Department of Obstetrics and Gynecology at Stanford University. After attending Harvard Medical School, he completed his residency in obstetrics/gynecology at Stanford and his fellowship in reproductive endocrinology at the University of California, San Francisco. Board certified in reproductive endocrinology and infertility, Dr. Cataldo has cared for patients with fertility and ovulation disorders and has been active in

both basic and clinical research on ovarian function. His major interest and recent publications center around polycystic ovarian syndrome and therapies for the ovarian abnormality that leads to ovulation failure in this disorder.

Marcelle Cedars, M.D., is professor, director of the Center for Reproductive Health and Reproductive Laboratories, and vice-chair of clinical affairs, all in the Department of Obstetrics and Gynecology at the University of California, San Francisco. In the past, she has been director of IVF programs and/or laboratories at the University of California, Los Angeles, the University of Cincinnati, and the University of Colorado Health Sciences Center. She is board certified in both reproductive endocrinology and obstetrics and gynecology. She has served on the Editorial Board of *Fertility and Sterility* and is currently a member of the Division of Reproductive Endocrinology for the American Board of Obstetrics and Gynecology and is the chair of the U.S. Food and Drug Administration's Panel on Obstetrical and Gynecological Devices. Dr. Cedars received her M.D. from Southwestern Medical School. Her clinical and research endeavors involve polycystic ovarian syndrome, perimenopause, and assisted reproduction.

John Collins, M.D., is professor emeritus at McMaster University and adjunct professor at Dalhousie University. He was department chair at McMaster University from 1983 to 1993 and acting chair from 1996 to 1998. His clinical practice involved reproductive endocrinology and infertility. Dr. Collins received his M.D. and postgraduate training in Obstetrics and Gynecology from the University of Western Ontario. A previous member of the editorial boards of the *New England Journal of Medicine*, *Fertility and Sterility*, *Human Reproduction Update* and *Evidence-Based Medicine*, he is now on the Editorial Board of *Obstetrics and Gynecology* and is an associate editor of *Human Reproduction*. He is a former president of the Society of Obstetricians and Gynecologists of Canada, the Canadian Fertility and Andrology Society, and the Association of Professors of Obstetrics and Gynecology. He is currently a consultant to the Practice Committee of the American Society for Reproductive Medicine. Dr. Collins's research, which has been reported in more than 150 peer-reviewed publications, involves the evaluation of outcomes, such as the effectiveness, safety, and cost of interventions for reproductive health disorders and the long-term cardiovascular and can-

cer outcomes associated with use of oral contraception and hormone treatment.

David Guzick, M.D., Ph.D., is dean of the School of Medicine and Dentistry at the University of Rochester. He was the Henry A. Thiede professor and chair of obstetrics and gynecology at the University of Rochester from 1995 until 2002. He is also former director of reproductive endocrinology at Magee Women's Hospital at the University of Pittsburgh. Dr. Guzick received his graduate degrees from New York University and is board certified in obstetrics and gynecology and reproductive endocrinology. He has served on several National Institutes of Health scientific advisory committees. Dr. Guzick has published extensively on infertility and reproductive endocrinology.

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Roberta B. Ness, M.D., M.P.H., is professor of epidemiology, medicine, and obstetrics/gynecology at the University of Pittsburgh. She is chair of the Department of Epidemiology and director of its Women's Health Program. She was previously assistant professor at the University of Pennsylvania and director of cancer epidemiology at the University of Pittsburgh Cancer Institute. Dr. Ness received her M.D. from Cornell University and her M.P.H from Columbia University. She has served on various scientific advisory committees on women's health. Her specific areas of interest include studies in the epidemiology of reproductive cancers, preeclampsia, and pelvic inflammatory disease.

Lawrence Ching Tsen, M.D., is associate professor in anesthesia at Harvard Medical School and director of anesthesia at the Center for Reproductive Medicine, Brigham and Women's Hospital. He is on the Editorial Board of the journals *Obstetric Anesthesia Digest* and *International Journal of Obstetric Anesthesia*. He is also an active member of the Society for Obstetric Anesthesia and Perinatology, the Massachusetts Society of Anesthesiologists, the American Society for Anesthesiologists, and the International Anesthesia Research Society. Dr. Tsen received his M.D. from the University of Kansas School of Medicine. His research aims to improve the quality and safety of obstetric analgesia and anesthesia.

STAFF

Amy Haas is the administrative assistant for the Board on Health Sciences Policy. She previously served as a senior project assistant for the Clinical Research Roundtable. Prior to joining the Institute of Medicine, she worked as a project manager for a medical education and publishing firm in Washington, DC. She graduated from Whitman College in Walla Walla, Washington, with a B.A. in biology.

Andrew Pope, Ph.D., is director of the Board on Health Sciences Policy at the Institute of Medicine. With expertise in physiology and biochemistry, his primary interests focus on environmental and occupational influences on human health. Dr. Pope's previous research activities focused on the neuroendocrine and reproductive effects of various environmental substances on food-producing animals. During his tenure at the National Academy of Sciences and since 1989 at the Institute of Medicine, Dr. Pope has directed numerous studies; topics include injury control, disability prevention, biologic markers, neurotoxicology, indoor allergens, and the enhancement of environmental and occupational health content in medical and nursing school curricula. Most recently, Dr. Pope directed studies on priority-setting processes at the National Institutes of Health, fluid resuscitation practices in combat casualties, and organ procurement and transplantation.

Eileen Santa, M.A., has been a research associate at the Institute of Medicine for two years. She earned her masters in clinical psychology from the University of Massachusetts, where she is currently a doctoral

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Frances E. Sharples, M.A., Ph.D., has served as the director of the National Research Council's Board on Life Sciences since October 2000. Immediately prior to this position, she was a senior policy analyst for the Environment Division of the White House Office of Science and Technology Policy (OSTP) for four years. Dr. Sharples came to OSTP from the Oak Ridge National Laboratory, where she served in various positions in the Environmental Sciences Division between 1978 and 1996, most recently as a research and development section head. Dr. Sharples received her B.A. in biology from Barnard College and her M.A. and Ph.D. in zoology from the University of California, Davis. She served as an American Association for the Advancement of Science (AAAS) environmental science and engineering fellow at the Environmental Protection Agency during the summer of 1981, and as a AAAS congressional science and engineering fellow in the office of Senator Al Gore in 1984-1985. She was a member of the National Institutes of Health's Recombinant DNA Advisory Committee in the mid-1980s and was elected a fellow of the AAAS in 1992.