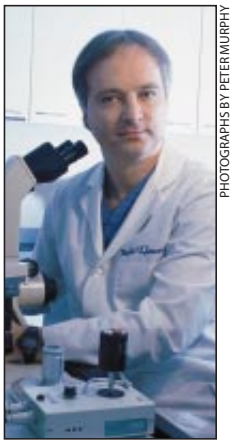
Q&A

Infertility

Zev Rosenwaks, M.D.



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Mark V. Sauer, M.D.

Since 1978, when the first test-tube baby was born, infertility treatments have become widespread. Today 315 fertility clinics operate in the U.S., offering infertile women and men an array of expensive, high-tech procedures with acronyms like IVF (in vitro fertilization), GIFT (gamete intrafallopian transfer) and ICSI (intracytoplasmic sperm injection). Aided by IVF and other procedures, 72,000 babies have been born in the U.S., according to the American Society for Reproductive Medicine, and about 15 percent of American women have sought some type of infertility treatment. The increasing demand for infertility treatments has been partly spurred by the aging of the baby boom generation. About 6.1 million women in the U.S., or 10 percent of the women of reproductive age, are now infertile, compared with 4.9 million in 1988, as reported by the National Center for Health Statistics.

Nearly every advance in the treatment of infertility generates ethical dilemmas and controversy. Two pioneers in the field are **ZEV ROSENWAKS, M.D.,** *professor of obstetrics and gynecology and director of the Center for Reproductive Medicine and Infertility at New York Hospital–Cornell Medical Center, and* **MARK V. SAUER, M.D.,** *professor of obstetrics and gynecology at Columbia University and director of reproductive endocrinology at Columbia-Presbyterian Medical Center. In the following interview,* **MARJORIE SHAFFER,** *special correspondent for* SCIENTIFIC AMERICAN, *talks to these doctors about the latest advances and dilemmas in the treatment of infertility.*

Q *What are the most common causes of infertility today?*

A **ROSENWAKS:** That depends on the demographics in the area that a fertility clinic serves. In our clinic, the most common reasons are male infertility caused by problems with a man's sperm or female infertility caused by endometriosis, ovulatory dysfunction and advanced maternal age.

SAUER: Age-related infertility is an increasingly common reason women seek fertility treatments. Ten years ago maybe 5 percent of my patients were around the age of 40; today probably 80 percent of my patients are between the ages of 40 and 50. Many of these women have nothing wrong with them, except that they are older. The likelihood of a successful pregnancy in a woman over the age of 45 using her own eggs is very low. But using donor eggs, success rates are unaffected by age: women over the age of 45 have the same likelihood of giving birth as 35-year-old women. According to registry data from the Society for Assisted Reproductive Technology, since 1990 there has been more than a 10-fold increase in the number of women over 40 receiving IVF and a nearly 10-fold rise in the number of egg donations.

Last year Reproductive Biology Associates (RBA), a fertility clinic in Atlanta, reported that a woman gave birth to twin boys conceived with donor eggs that had previously been frozen. Is this a breakthrough? How will it affect the treatment of infertility?

ROSENWAKS: Ethically, it is much more acceptable to freeze gametes—eggs and sperm—than embryos. We do freeze eggs for women who have cancer and will undergo chemotherapy, but we tell them this is far from an efficient procedure. There is no guarantee that we can preserve their ability to reproduce. One needs to put this latest news of egg freezing, as encouraging as it might be, into perspective. The chances of achieving a pregnancy with each previously frozen egg is probably no greater than 2 percent. This is still an area that requires further refinement. I hope healthy young women don't see egg freezing as a convenient way to bank their eggs for use 20 years later.

SAUER: I think the Atlanta births promise to be a big breakthrough. We have been approached by two sets of patients who want to freeze their eggs. The first are women who are ill and want to preserve their reproductive capacity because treatments

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like chemotherapy damage the ovaries. The second are professional women in their mid-30s who are becoming aware of the reproductive hazards of aging and have no desire to bank embryos but think they might want to use their eggs later with a husband or boyfriend. Despite the demand, many eggs never survive the freezing process. The good news is that along with RBA, two groups in Italy have had successful pregnancies using previously frozen eggs. So I think we will continue to improve the technology, and eventually it will become commonplace.

Making Parents

Assisted reproductive technologies have enabled women well past menopause to give birth to children conceived with donor eggs. Is there an age beyond which a woman can no longer give birth?

ROSENWAKS: Theoretically, it is possible for a 70-year-old woman to have a baby. But we have a responsibility to safeguard the health of the woman and her baby. Nothing is guaranteed in life, but is it fair for a child to be born to a couple in their 70s? How long will that child have with his or her parents? We usually only treat women of reproductive age, meaning up to the age of menopause.

SAUER: I have treated well over 100 women in their 50s, and they have done extremely well, even those who gave birth to triplets. But it is a very biased cohort of patients; they are very healthy. We usually won't treat women over the age of 55 unless there are compelling reasons. In the last year we had three women over that age: they were 57, 59 and 61. The two women in their 50s already had babies through IVF in my practice and wanted another child. These women were healthy, and I saw no reason not to help them again. And what was the compelling reason for the 61-year-old woman? Well, she lied about her age. We thought she was quite a bit younger. When a woman over the age of 55 comes to see me, our department's ethics committee and many other staff members discuss the merits of her particular case. If a woman older than 55 has survived cancer, for example, and she couldn't conceive when she was younger because she was getting treated for cancer, we would probably treat her, if she understands the risks.

Some reproductive immunologists contend that some women have repeated miscarriages because they produce antibodies that interfere with the growth of the placenta or the embryo. These specialists say that aspirin, the anticoagulant heparin and intravenous immunoglobulins can counteract such antibodies. Do such immunotherapies offer hope to childless couples?

ROSENWAKS: There is compelling evidence that genetics plays an important role in IVF failure, but it is difficult to understand how immunological rejection does. In our clinic, we get very high pregnancy rates without immunological treatments. There is no doubt, however, that in specific cases you can demonstrate an immunological reason for miscarriage. But one needs to be careful to tailor treatment to the findings. You have to be cautious; immunotherapies have to be tested in clinical trials. In our hands, at least in preliminary work, we have administered heparin or aspirin—both of which can prevent clotting abnormalities in developing embryos and are considered immunotherapies—to women for whom IVF has failed, and we haven't observed that the drugs have made any contribution to the success or failure of IVF.

SAUER: Immunotherapy is a very controversial field. If you look at a well-defined population of women who have had recurrent miscarriages, there is certainly a subgroup that has persistently high levels of antibodies. But the panels of tests for detecting these antibodies are very expensive, and immunotherapies aren't innocuous, making it harder and harder for patients and their physicians to know what to do. We have had some success with the therapies, but they are still not proved in clinical trials.

Some researchers believe that many cases of male infertility are the result of genetic defects and that ICSI might promote the transmission of these defects by allowing defective sperm to fertilize an egg. Is this concern warranted, and how it is being addressed?

ROSENWAKS: There is a higher frequency of genetic deletions in the Y chromosome that may or may not be associated with infertility in men with severe oligospermia, or below-normal sperm counts. Sons conceived with the aid of ICSI will have the same genetic abnormality as their fathers. We recommend that all men with severe oligospermia undergo genetic testing; about 10 percent will have deletions or other chromosomal abnormalities. These aren't lethal defects. Men often tell us, "Well, I have it, so the worst that will happen is that my son will have it." But men who have a congenital absence of the vas deferens, the duct that carries semen from the testes, also carry the gene for cystic fibrosis. Before implantation into the uterus, we recommend genetic testing of all embryos conceived with the sperm of men who lack the vas deferens. This is an important area of investigation because these men can transmit the cystic fibrosis gene to their children.

SAUER: Men who are sterile or subfertile might carry deleterious genes that through natural selection wouldn't be passed on. We now know that 5 to 15 percent of infertile men have definable Y chromosome deletions associated with infertility.

The ABCs of ART

(Assisted Reproductive Technology)

IVF In vitro fertilization. Eggs are removed from a woman's ovary and are fertilized by a man's sperm in the laboratory. The resulting embryos are then transferred into the woman's uterus. The procedure is used in some 70 percent of assisted reproduction procedures, according to the latest statistics available from the U.S. Centers for Disease Control and Prevention (CDC).

ICSI Intracytoplasmic sperm injection. One sperm is injected directly into an egg in the laboratory to achieve fertilization. The embryo is then transferred into the uterus. The technique has been used since 1992 to conquer the problem of low sperm counts, sperm with little movement or sperm that cannot penetrate an egg. According to the latest CDC statistics, roughly 11 percent of assisted reproduction procedures include ICSI.

GIFT Gamete intrafallopian transfer. Eggs are removed from a woman's ovary and are placed, along with sperm, into the woman's fallopian tubes, where fertilization takes place. GIFT is used in only 6 percent of assisted reproduction procedures, as reported by the CDC. —*M.S.*

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Perhaps these deletions are linked to other disorders yet to be unmasked that will become more common as generations of ICSI-conceived sons are born. There are places in the world, like the Netherlands, where ICSI has been put on hold because they want to have a national debate before they initiate care. The good news is that to date there doesn't appear to be an increase in pregnancy loss or chromosomal abnormalities affecting sons conceived through ICSI. But these children are young. We would be more reassured if we followed these children for 20 years and there still wasn't an increase in abnormalities.

Will it ever be possible for a man who produces no sperm at all to father a child?

ROSENWAKS: Yes. I think that in the future we may be able to create a spermlike cell from a normal body cell by using cloning technology. This would be a different process than the one used to make Dolly the sheep. Everybody talks about how cloning shouldn't be done to make an identical individual, and we agree. But—and this is just speculation—let's say that you could take a normal body cell from a man and transplant it into an egg that had had its nucleus removed and induce it to divide in such a way that the resulting cells would have only half the number of chromosomes as the original cell, like sperm and eggs. These cells could be used to fertilize an egg through IVF. I think this use of cloning technology is much more akin to natural reproduction. The transformed cell would undergo recombination, or genetic reshuffling, the same way as any sperm cell, and therefore this process would be devoid of the potential social and biological risks of cloning.

Risks and Trade-offs

The use of fertility drugs in assisted reproduction has led to an enormous rise in the number of multiple pregnancies because many embryos have to be put into a woman's uterus to ensure a successful pregnancy. What strategies—besides selective abortion of one or more embryos—are being developed to improve the chances that only one child will be born as a result of IVF and other assisted reproductive technologies?

ROSENWAKS: Theoretically, if you could identify the embryo in the laboratory that has a high likelihood of implantation, then you could transfer one, at most two, embryos. If you could nourish embryos in improved media and grow them in the laboratory with the cells that embryos ordinarily encounter in the uterus, then you could transplant the embryo into the uterus when it is five days old, when it has the best chance of implanting. We have established a system where we use the mother's own endometrial, or uterine lining, cells previously obtained during a natural menstrual cycle.

SAUER: This is an avant-garde area of research. The reasons we transfer multiple embryos at 48 or 72 hours of age relate to the culture media and laboratory conditions, which have always been suboptimal. It becomes more perilous for the embryo after two or three days. But if we can delay the implantation until the embryo is five days old, when it is more developed, then we could transfer only two or three embryos into the uterus. At that stage of development, embryos have the best chance of implanting. We are working on a strategy called staged culture media, in which the technician changes the culture medium as the embryo gets further along, allowing the embryo to grow more efficiently to the five-day stage.

Assisted reproduction is an expensive process. One cycle of IVF costs $8,000, and most insurers in the U.S. won't cover the cost. What is needed to bring the cost down to more affordable levels?

ROSENWAKS: Society and government should look at IVF as a practical, efficient way of treating the important medical problem of infertility. And the government should fund research and development in this field so that these costs will not be added to the cost of IVF. IVF is a labor-intensive endeavor, however; you don't just perform surgery for an hour. You treat the patient for three weeks to a month at a time; the patient has multiple blood tests and ultrasounds and has eggs retrieved. These procedures require many nurses, technicians, embryologists and physicians. This is expensive. But if you look at the cost efficiency per baby, IVF in properly selected patients is probably less expensive than other treatments for infertility. Consider a woman who has undergone surgery to remove blockages in her fallopian tubes. If that surgery doesn't solve her infertility problem, then she and her husband may wish to try IVF, which can lead to the birth of a child. If you compare the cost of the surgery and IVF, then IVF would be more cost-effective.

SAUER: I would prefer to see universal coverage for infertility. But the question is, Who will pay for it? There is little that will keep these costs down; if anything, the costs will continue to rise. There is a lot of money being made. It isn't just physicians who drive this, but pharmaceutical companies as well, which have continually raised the price of their products to whatever the market will bear. To me, it is sort of a sad commentary on this field of medicine. The field is becoming a lot like plastic surgery—whoever can afford it will get it. We have fought government regulation, believing that physicians should regulate themselves. But I am concerned now that we are just kidding ourselves. I am starting to rethink whether it is time for the federal or state governments to say enough already, let's figure out a way to get patients the treatments they need in a cost-effective, reasonable way.

It seems that most infertility treatments involve medical procedures for the woman, even if it's the man in the couple who's infertile. Why isn't more known about male reproductive biology?

SAUER: This is a valid question. Is there sexism being practiced in this field? I think there is. Perhaps women are more willing to endure the probing, sticking and general invasiveness of many infertility-treatment procedures. Most men would never put up with it. The male reproductive system also is a lot more redundant than a woman's. There are millions, if not billions, of sperm, and you can have an awful lot wrong with a man's anatomy and physiology and he can still father a child. Nature is less forgiving to women.

Has there been any long-term follow-up of the thousands of children born worldwide with the aid of assisted reproductive technologies? Are these children more likely to have certain health problems?

ROSENWAKS: More than 4,300 children have been conceived through IVF just in our clinic alone. In the small studies that have looked at children at one to two years of age, IVF had no deleterious impact on their general health and intelligence. No matter what you do in medicine, it is desirable to follow up on the consequences of any procedure. But there have been hundreds of thousands of babies born through IVF, and I don't

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think there is any reason to believe that there would be long-term health problems in these children.

SAUER: I don't think there are any large population studies of IVF-conceived children, and there is a good reason for that. A lot of people have gone through such hell to have a child this way, and they are so relieved not to have to think about it anymore that they are not too compliant in follow-up studies. Most of the studies have been done in young children, and there doesn't appear to be anything different about these families, other than a lot of multiple births. When you get triplets in a family, there are a lot of unique stresses. But I don't think there is much to be concerned about. SA

Endometriosis: A Major Cause of Infertility in Women

Some women experience severe abdominal pain, nausea, vomiting, bloating, and heavy or irregular bleeding during their periods. For others, the only symptom is infertility. Still others have terrible cramping pains during their periods but can become pregnant readily.

The problem all these women share is endometriosis, a disease of the reproductive system that is largely a mystery despite the fact that it afflicts between 3 and 10 percent of all women of reproductive age. But despite its prevalence, many women with endometriosis remain undiagnosed because there are no biochemical markers for the disease that can be detected in the blood or urine.

Researchers are now looking for the cause of endometriosis, which renders between 30 and 40 percent of the women who have it infertile. Understanding the cause will allow better diagnosis and treatment.

Endometriosis occurs when the tissue lining the uterus, which is called the endometrium, detaches itself and takes up residence in the abdomen outside the uterus, perhaps by traveling up through the fallopian tubes. This roving (endometriotic) tissue usually plants itself near the ovaries, on the outer surface of the uterus, in the cul-de-sac behind the uterus and in the area between the vagina and the rectum. The growths can also be found on the outside of the fallopian tubes; on abdominal surgery scars, the intestines and the bladder; and even in such far-flung places as the lungs, arms and brain.

The pain of endometriosis results because the transplanted tissue continues to swell and bleed in response to the same hormonal cues as normal endometrial cells during the menstrual cycle. But, unlike the normal cells, which are flushed out of the body each month during menstruation, the transplanted tissue has no place to go—it remains inside the body, causing adhesions, inflammation and scarring.

Many questions about endometriosis remain unanswered. Researchers still don't know why some women with mild endometriosis are able to get pregnant while others can't. Severe endometriosis is easier to understand: infertility occurs because the fallopian tubes are blocked or the ovaries have sustained damage.

"This is such an enigmatic disease," says Sandra A. Carson, professor of obstetrics and gynecology at Baylor College of Medicine. "Pain and other symptoms may not correlate at all with the size of the endometrial growths. We need to understand the stages of this disease and their association with molecular signals. And we need to have a marker in the blood that we could use to diagnose this disease."

Although no one theory can account for all cases of endometriosis, in the late 1980s the notion that retrograde menstruation is a cause of the disease gained supporters. According to this theory, menstrual tissue backs up through the fallopian tubes during menstruation and into the abdomen, where it adheres and proliferates.

Yet of the 75 to 95 percent of all women who experience retrograde menstruation, only some develop endometriosis. "In the past, we hypothesized that there must be something wrong with the immune system of women who develop a disease that allows transplanted endometriotic cells to grow outside the uterus," says Serdar E. Bulun, professor of obstetrics and gynecology at the University of Texas Southwestern Medical Center at Dallas. "But then we started to ask whether there was something distinctly different in the transplanted tissue itself that allows endometriosis to develop."

Once researchers turned their attention to the transplanted endometriotic tissue, they began discovering many differences between the transplanted cells and normal cells. Some groups have found increased concentrations of inflammatory proteins and other components of the immune system in the transplanted endometriotic cells, whereas others have identified proteins that might uniquely identify the cells.

These findings may lead to new therapies and to diagnostic markers in the blood. Currently the only way to diagnose endometriosis is through laparoscopy, a surgical procedure in which the abdomen is viewed through a tubelike instrument with a light attached.

Some of the recent findings about endometriotic transplants are leading to novel ideas about how the disease occurs. Bulun and his colleagues, for example, have detected high levels of an enzyme called aromatase in the transplants. Aromatase is a key player in a series of reactions leading to the production of the hormone estrogen, which can sometimes provoke endometrial cells to proliferate and cause cancer.

Bulun's group has found that aromatase levels in transplanted endometriotic tissue are as high as levels of the enzyme in the ovaries, where estrogen is produced. "This transplanted tissue is devious enough to make its own estrogen," he says. "The estrogen is like fuel. If you cut the supply, the tissue will stop growing."

Bulun speculates that hormonelike chemicals called prostaglandins, which are found in the abdominal cavity and elsewhere, cause aromatase in transplanted endometriotic tissue to go into overdrive and produce more estrogen. Prostaglandins play a wide variety of roles but are implicated in many of the symptoms of endometriosis, especially pain.

Traditional treatments for endometriosis, such as the drug danazol or gonadotropin-releasing hormone agonists, inhibit the production of estrogen in the ovaries. But Bulun says some women with severe endometriosis don't respond to these treatments, because the drugs don't stop estrogen production in endometriotic transplants outside the uterus. His group is developing aromatase inhibitors that might become new treatments for the disease.

Still, some researchers doubt there will prove to be a single magic bullet for endometriosis. "We have lots of abnormal findings, and it isn't clear which of them is the cause and which the effect," says David L. Olive, professor of obstetrics and gynecology at the Yale University School of Medicine. He adds that the aromatase link "is a start, but what we need now is to prove a cause-and-effect relationship for the disease." —*M.S.*

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