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Reproductive Technology

In the United States, infertility is a concern for many couples of childbearing age. Infertility as defined in a study or official analysis consists of the absence of pregnancy in the 12 months prior to an interview or medical encounter, despite having had unprotected sexual intercourse in each of those months with the same partner. Many couples who desire to have a child seek assistance through reproductive technology. These methods include fertility treatments in which eggs or embryos are handled in the laboratory—that is, through in vitro fertilization (IVF)—to form a combined cell known as a zygote from an egg and sperm.

According to 2011–2015 data from the Centers for Disease Control (CDC), nearly 7% of married women aged 15–44 were infertile, and 7.3 million women in that age group had used infertility services. Infertility concerns also extend to men. In about 35% of couples with infertility, a male factor is identified together with a female factor. CDC data from 2006–2010 showed that 12% of men aged 25–44 reported some type of infertility and believed that it would be impossible or difficult for them to father a child—an increase from the rate of 9% in the 15–44 age group.

Since the first US infant conceived with assisted reproductive technology (ART) was born in 1981, the use of such methods and the number of fertility clinics providing reproductive technology services has increased steadily. By 2015, such procedures had led to more than 1 million babies being born in the United States. Newer and less invasive ways to genetically test IVF embryos and immature eggs (oocytes) for various abnormalities before they are implanted not only help lower the risks of transmitting genetic defects to offspring, they also reduce the risks of failed implantation and pregnancy loss (called miscarriage).

Pregnancy and Infertility

Successful pregnancy first requires ovulation (when an ovary releases an egg into a fallopian tube), transport of the egg partway down the fallopian tube, movement of sperm from the vagina to the fallopian tube, penetration by the sperm of the egg’s protective layer, and implantation of the fertilized egg in the uterus.

Many factors lead to infertility. Disorders among men account for 30% of fertility problems in couples, including tube blockages and poor sperm quality, movement (motility), and quantity. Disorders among
women account for another 45% of problems and include endometriosis (a disorder of the lining of the uterus called the endometrium), ovulation problems, tube blockages, poor egg quality, and hormone imbalances. The causes of fertility problems are unexplained in 25% of couples and are due to a combination of male and female factors in about 40% of couples seeking treatment. Sexually transmitted infections, such as those caused by the organisms Chlamydia trachomatis and Neisseria gonorrhoeae, may lead to scarring and tube blockages. And an estimated 12% of all infertility cases result from the woman weighing too little or too much, with about the same percentage of infertility caused by cigarette smoking.

Many couples can overcome infertility through hormonal or surgical interventions. Women experiencing ovulation disorders may benefit from treatment with oral drugs (such as clomiphene citrate) or through the injection of hormones called gonadotropins, such as follicle-stimulating hormones, which stimulate the growth and maturation of ovarian follicles that, in turn, produce the primary sex-related hormone estradiol. The success rate depends on many factors, including the health and age of the parents, and a higher chance of multiple births exists. Some women with tubal disease can be helped by various types of reconstructive surgery, although the success rate is often lower than would be achieved using ART and may not be appropriate for women older than 35 years of age.

Nevertheless, many infertile couples cannot be helped by standard treatment methods. In such cases, couples wanting children may turn to newer techniques that bypass one or more steps in the usual processes of ovulation, fertilization, and implantation. ART techniques include fertilization that takes place under laboratory conditions rather than within a living organism, known as in vitro (Latin for “in glass”) fertilization (IVF). Other methods include gamete intrafallopian transfer, zygote intrafallopian transfer, donor insemination, egg donation, embryo cryopreservation (using very cold temperatures to preserve a sample), intracytoplasmic sperm injection, tubal embryo-stage transfer, and intrauterine insemination.

**In Vitro Fertilization**

When performed by an experienced practitioner and in a clinic that adheres to high-quality standards, IVF generally has about a 45% chance of resulting in pregnancy in women younger than 35 years. The process involves the five major steps of ovarian stimulation, egg retrieval, fertilization, embryo culture, and embryo transfer.

Generally, one attempt at IVF is made per menstrual cycle, at an average cost of $10,000–15,000. The IVF process begins when couples are first screened. Clinicians first must rule out infertility in the male partner. If the problem is with the female partner, various courses of treatment may be available. Generally, couples are expected to try to achieve pregnancy for a year after the initial screening before intervention is attempted.
However, if a woman is in her late thirties or older, or if she is experiencing irregular menstruation, a clinical investigation may begin earlier.

Blood levels of follicle-stimulating hormone, a hormone that acts on the ovary to stimulate the maturation of viable eggs, are measured, especially in older women. If the hormone’s level is elevated early in a woman’s menstrual cycle (after the first week of the new cycle), her ovaries may not be responding to it. In that case, hormonal treatment to stimulate ovulation would be ineffective, and assisted reproductive technology would be unable to help achieve pregnancy. High estrogen levels at day three would also indicate that the ovaries are not responding correctly to estrogen or hormones.

In women whose ovaries are capable of generating viable eggs—that is, eggs that can survive—the first step in IVF is ovarian stimulation, which uses oral or injected medications, also known as fertility drugs. To increase the chance of success, the drugs stimulate the ovaries to develop many follicles, which contain maturing eggs. Normally, only one or perhaps two follicles develop and are released by an ovary during a single menstrual cycle, which is why usually only one or, on rare occasions, such as fraternal twinning, two children are born. With ovarian stimulation by medications, multiple follicles are induced to develop so that many oocytes can be collected.

To stimulate the ovaries to develop many follicles, the action of the pituitary gland is suppressed hormonally, and 10 days later the woman is treated with follicle-stimulating hormone. To see how well her ovaries are responding to the hormone, doctors measure estrogen blood levels and observe the ovaries with ultrasound scans that use sound waves. The number and size of the follicles can be visualized. About 8 to 14 days later, when the follicle is enlarged to the point that it protrudes above the surface of the ovary, the woman is given human chorionic gonadotropin, which should allow the eggs to be fertilized. After about 36 hours, the eggs can be retrieved before ovulation occurs.

Next, the eggs are obtained under ultrasound guidance using an aspiration method that removes the eggs from the follicles through a needle inserted through the vagina. The doctors may collect up to 11 oocytes from a single patient. Once retrieved, the eggs are inspected under the microscope for maturity and quality and are held in a nutrient medium in an incubator before fertilization.

Viable sperm are collected from the man following self-stimulation or through the use of a special condom used during intercourse. The sperm are washed in a solution that activates them so that they can fertilize the egg. The sperm activation process is called capacitation and normally occurs when sperm are ejaculated and enter the female reproductive tract. Capacitation involves activating enzymes in the sperm cell tip, called the acrosomal cap, which contains digestive enzymes for penetrating the egg, thus allowing the sperm head (containing the sperm’s genetic material) to penetrate the outer and inner membranes surrounding the outer cell surface of the egg (the zona pellucida and vitelline membrane, respectively).
For males lacking sperm in their ejaculates (a condition called azoospermia), microsurgical or aspiration techniques can directly extract sperm from either the curved tube called the epididymis, where sperm are stored and mature, or from the testicles themselves. Azoospermia is the most severe form of male infertility, caused by obstructions in the genital tract or by testicular failure.

If successful fertilization is less likely, as may occur with poor semen quality or prior IVF cycle failure, the sperm may instead be directly injected into each mature egg. This process, called intracytoplasmic sperm injection (ICSI), fertilizes about one-half to three-quarters of injected eggs, though the fertilized egg may fail to grow and may not develop into an embryo. A fertilized egg is allowed to grow for about five days in the laboratory before being transferred to the female uterus, sometimes called the womb.

If inherited abnormalities are suspected that may be passed from father to son, the couple may be offered genetic counseling before ICSI is attempted. For example, abnormal sex chromosome (X and Y) number has been observed in the sperm of men with abnormal semen analysis. Abnormal chromosome number (aneuploidy) of the sex chromosomes of children conceived via ICSI is slightly higher than that observed in the general IVF population (0.8% to 1.0% in ICSI offspring versus 0.2% in the general IVF population). Men with very low to absent sperm counts may have minute areas on the Y chromosome where genetic information is missing, called Y chromosome microdeletions. Male offspring conceived through ICSI from fathers whose infertility was genetically based owing to such microdeletions may therefore also develop infertility.

Otherwise, if ICSI is not used, a single egg and about 100,000 sperm are placed together to allow fertilization to take place. The mixture is incubated and kept in a special culture medium for about 24 hours. By microscopy, the presence of two pronuclei (one from the egg and one from the sperm) in the egg indicates that fertilization has occurred. By the third day after fertilization, the growing embryo will contain only about six to ten cells. When, around the fifth day, a fluid-filled cavity begins to form within the embryo, along with an outer layer of early placental tissue called the trophoblast, the embryo is called a blastocyst. The developing embryo may be transferred to the uterus anytime from one to six days after the eggs are obtained. Provided development continues normally, the embryo will hatch from its protective outer layer and enter (implant into) the lining of the uterus, usually from six to ten days after egg retrieval. However, in some cases, sperm may have been unable to penetrate and fertilize the egg. They might have been unable to swim correctly or might not have been capacitated successfully. Any extra embryos that remain after a successful embryo transfer to the uterus can be saved for possible future use for up to almost 20 years through the cold storage technique of cryopreservation. Young women who face cancer treatment such as chemotherapy have the option of cryopreserving their unfertilized eggs. Sperm may also be cryopreserved.
A number of factors contribute to whether embryo transfer leads to a baby being born. The success rate is higher if embryo transfer takes place between 48 and 72 hours after oocyte collection. When more than one embryo is transferred at the same time, the success rate increases, but so does the chance for multiple pregnancies. Depending on various couple-specific factors, such as age and prior IVF attempts, about two to five embryos may be transferred. Probably the single most important factor determining whether or not a successful embryo implantation will take place is the donated egg’s age. Unlike sperm that are made throughout male reproductive life, the making and maturation of female sex cells, called oogenesis, is arrested around the time of birth. When females enter puberty, immature eggs called primary oocytes resume the specialized cell division of meiosis to produce a mature, fertilizable egg during each menstrual cycle. Embryos formed from eggs donated by younger women have a higher implantation success rate than do embryos formed from eggs donated by older women. The age of the host uterus appears to have little or no effect on outcome.

The Risks of IVF

In some women, the drugs used to stimulate the ovaries may cause side effects, including discomfort, fluid accumulation, and mood swings. Less than 2% of women develop more severe complications, such as dangerous and excessive fluid accumulation, blood clots, and kidney failure. Complications also may arise as a result of the surgical procedures involved in egg retrieval and embryo transfer. These problems can include pelvic and other infections, complications from anesthesia, and internal injuries such as bleeding and organ damage. Although the incidence of
such complications is low, every chemical or surgical intervention is associated with risks, about which potential patients must be informed.

IVF carries the risk of multiple pregnancy, especially when more than one embryo is transferred. As a result, a woman carrying a multiple pregnancy may need to adhere to strict bed rest to avoid delivery before reaching term, which normally extends to around nine months. If the multiple-birth babies are born before term, they may require intensive care or be at a survival disadvantage.

**Other Assisted Reproductive Technology Methods**

Less than 1% of ART procedures are performed by gamete intrafallopian transfer (GIFT), a procedure in which both eggs and sperm are transferred to the woman’s fallopian tube. This allows fertilization to take place in the tube rather than the laboratory, which may satisfy some faith-based concerns. GIFT can only be performed in women with healthy, functional fallopian tubes, and the sperm used for fertilization must be normal and capable of swimming. Additionally, GIFT requires laparoscopy, a more extensive minimally invasive surgical procedure performed using small entry ports and cameras rather than through a larger surgical incision. Unlike the traditional IVF, fertilization cannot be confirmed with GIFT. A variation on GIFT is zygote intrafallopian transfer (ZIFT), in which the egg is fertilized in the laboratory but instead of being allowed to partly grow and be transferred to the uterus, the zygote is placed in the fallopian tube. This procedure also requires laparoscopy and is less common than GIFT in the United States.

**Intrauterine Insemination**

Intrauterine insemination (IUI) is sometimes used when a couple’s inability to conceive a child is caused by the sperm’s inability to reach the egg. IUI is less expensive and less invasive than IVF. Sperm must move through the uterus and enter the fallopian tube before they can fertilize the egg. Anything that prevents the sperm from making this trip will block conception. Sex-related (coital) or ejaculatory disorders can limit the sperm’s travels, as, for example, among couples affected by spinal cord disorders, diabetes, or other conditions that lower erectile function and ejaculation. In addition, sperm antibodies in the female reproductive tract can kill the sperm, and sperm may be unable to penetrate the cervical mucus.

To help the sperm reach the egg with IUI, the female is treated with human chorionic gonadotropin to induce multiple ovulations. As an alternative, the procedure may be coordinated with the menstrual cycle, timed to expected ovulation. If induced, the number of follicles that are stimulated is monitored by ultrasound. Washed sperm from the male partner are concentrated and injected into the uterus through the cervical opening. The pregnancy rate varies with this procedure, although a pregnancy can result in up to 20% of attempts.
Donor Insemination and Egg Donation

Donor insemination may be used when the male partner’s sperm are incapable of fertilizing the egg. Usually this occurs if the male produces very few or no sperm. Sometimes, donor sperm is used when the male partner is the carrier of a genetic disorder that could be transmitted to the baby. Sperm donors should, in general, be between the ages of 20 and 35 (an age window for good sperm quality and number), and all should be screened for genetic disorders, such as cystic fibrosis, and for various types of chromosomal abnormalities and infectious diseases, including hepatitis, syphilis, cytomegalovirus, and HIV. As with the use of intrauterine insemination, the female partner undergoes ovarian stimulation to maximize the number of follicles released during ovulation. Pregnancy rates resulting from the use of donor insemination range from about 30% to 50% after ten inseminations.

Similar to donor insemination, egg donation is used when the woman cannot ovulate or is the carrier of a genetic disease. Egg donors are generally 22 to 30 years of age and must be screened for the same type of conditions as sperm donors. Donors are treated with drugs to stimulate ovulation, after which the eggs are fertilized with the sperm from the male partner and the embryos are transferred to the uterus of the female partner (though other procedures can also be used). Growth and development of the embryos then follow the natural processes.

Surrogacy and Cryopreservation

Surrogacy, in which a couple’s pregnancy is carried by another woman, can supply a couple with an alternative if the female partner cannot carry the baby to term in her own uterus or for male same-sex partners who seek to father children. In some cases, if a woman cannot supply the egg, sperm from her male partner can be used to inseminate the surrogate, known as a gestational surrogate or gestational carrier, who then carries the baby to term. Alternatively, if the female partner can produce her own egg, sperm from the male partner can be used to fertilize the egg, and the resulting pre-embryo can be transferred to the uterus of the gestational surrogate to grow and develop. To avoid legal controversies and before any final decisions are made, the sequence of events, arrangements, and expectations should be carefully reviewed and documented by all parties, in consultation with experts in the field.

Cryopreservation is a very cold freezing method that allows individuals or couples to sustain the option of having progeny by freezing their own gametes or embryos. Frozen sperm and embryos effectively retain their viability for many years. The use of frozen human blastocysts is associated with a 10 percent successful pregnancy rate. Oocyte freezing, once much less successful, has vastly improved with the use of vitrification, an alternative cryopreservation method that allows cryogenic cooling but without mechanical damage from ice. IVF pregnancy rates using frozen oocytes are now about the same as those achieved using fresh oocytes.
Recognizing evidence that modern egg-freezing methods had improved pregnancy success, the American Society for Reproductive Medicine (ASRM) and the Society for Assisted Reproductive Technology (SART) jointly declared in a 2013 practice guideline that they would no longer consider egg freezing experimental, a move supported the following year by the American College of Obstetricians and Gynecologists (ACOG). Nevertheless, these groups cautioned against nonmedical egg freezing, that is, the social use of egg freezing as a backup or as “fertility insurance” against an age-related decreased ability to conceive. They cited limited studies on the safety, efficacy, cost-effectiveness, and emotional risks of egg freezing for healthy reproductive-age women. Safety risks include the possibility of excess ovarian stimulation, which is sometimes complicated by the serious health problems previously described. In addition, pregnancy and procedures associated with ART carry increased risks with advancing age.

**Age as a Factor**

Age must be taken into account when couples are considering assisted reproductive technology. The woman’s age is the most important factor in determining whether a couple will have a live birth using ART after choosing to use the woman’s own eggs, called *nondonor eggs*. Of the ART cycles reported by clinics to the CDC in 2014 that used nondonor eggs, 37% of the cycles begun in women younger than 35 produced a live birth; but that percentage declined with increasing female age, dropping to 1% among women older than age 44. The reasons for this decline include lower success rates of ovarian stimulation and egg retrieval, fewer cycles that progressed to egg transfer, fewer transfers that reached pregnancy, fewer pregnancies that resulted in live births, and a higher rate of miscarriage.

Paternal age and the DNA integrity of sperm are other factors to consider. Sperm, especially that of men older than 40, show increased rates of DNA fragmentation, with negative effects on the success rates of IVF and ICSI. Sperm also undergo more divisions than eggs, and mutations arise because of the increased error rates of DNA copying and repair that occur with advancing age. Increased or decreased numbers of chromosomes (aneuploidy) is also more frequent in sperm from older men. The success rates of ART and early embryo development are also lower with older men.

**Preimplantation Genetic Testing**

Before implantation, genetic testing can be performed on eggs, fertilized eggs, or in vitro fertilized embryos to find out whether such cells contain chromosome abnormalities and DNA mutations. Only embryos or eggs without these changes are then used to begin a pregnancy. Preimplantation genetic diagnosis (PGD) is less controversial than preimplantation genetic screening (PGS). With PGD, cells are tested when there is a known chromosomal abnormality or a genetic defect carried by one or both of the
parents that might be passed down to an offspring through IVF. Examples include a parent who is a carrier for sickle cell anemia (an inherited blood disease of poor oxygen carriage) or when a couple has a family history of a disorder linked to the X chromosome. On the other hand, the goal of PGS is to detect aneuploidy or chromosome abnormalities of extra DNA copies known as *insertions* or DNA losses known as *deletions* that have arisen from parents who are believed to be chromosomally normal. One reason for such screening is that between 40% and 60% of preimplantation embryos are believed to be aneuploid. Patient groups that have been targeted for PGS include older women, couples who have had repeated pregnancy losses or IVF failures, and male partners with a severe form of infertility.

Preimplantation genetic testing techniques have continued to evolve since their early development in the 1980s. More recently, biopsy on five-to-six-day-old embryos has been preferred over older techniques using younger embryos that had led to less accurate results and lower implantation rates. More advanced and rapid techniques such as next-generation sequencing and whole-genome amplification can be used, which produce multiple copies of genetic material for further chromosomal and genetic analysis, including the use of detection molecules called *probes* to find known types of gene mutations. Despite the scientific advancement of the tests themselves, the usefulness of some types of preimplantation testing has been called into question following a 2007 report showing that, among older women, PGS did not improve IVF pregnancy and live birth rates. For example, the phenomenon of mosaicism, in which more than one type of cell population exists in an organism, may help explain why the results from a single biopsy of the trophoblast may not be representative of the entire embryo. Improved methods, such as less invasive sampling procedures and greater test reliability, should enhance the usefulness of future preimplantation genetic testing.

Cells can also be genetically tested before implantation to determine whether the recognition proteins on white cells, known as *surface antigens*, might be adequately compatible with another person. Called *human leukocyte antigen (HLA) matching*, this testing may be done in cases in which a relative (such as a sibling) affected by an inherited disease might need a bone marrow transplant from a sibling-to-be tissue donor. For example, IVF with HLA-match testing has been used successfully for affected siblings with Fanconi’s anemia, a blood disease in which the bone marrow does not make enough of all types of blood cells.

All preimplantation genetic testing is preceded by genetic counseling by individuals with specific training and certification in genetics and genetic counseling. Such individuals include certified genetic counselors and medical geneticists. The genetic counselor reviews the risks of having a child with a genetic disorder and the risks to the potential pregnancy by a test procedure. Counseling also covers technical and interpretation limitations of the test results, for example, the potential that a positive test result may be falsely positive and that a negative result could be incorrect.
Assisted reproductive technology (ART) encompasses a range of treatments and procedures that include the handling of human eggs (oocytes) or embryos for the purpose of establishing a pregnancy. Other types of reproductive intervention that do not involve egg or embryo manipulation include assisted insemination using sperm from either a woman’s partner or a sperm donor. Although each type of reproductive technology is associated with a range of ethical issues, the range of methods have brought hope to millions of couples whose ability to have children was hindered by decreased fertility or failure to sustain a successful pregnancy. The 1978 birth of the first baby conceived using laboratory methods called in vitro fertilization (IVF) captured worldwide attention, inspiring