AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

Assisted Reproductive Technologies

A Guide for Patients

PATIENT INFORMATION SERIES

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ASSISTED REPRODUCTIVE TECHNOLOGIES

A Guide for Patients
Revised 2011

A glossary of italicized words is located at the end of this booklet.

INTRODUCTION

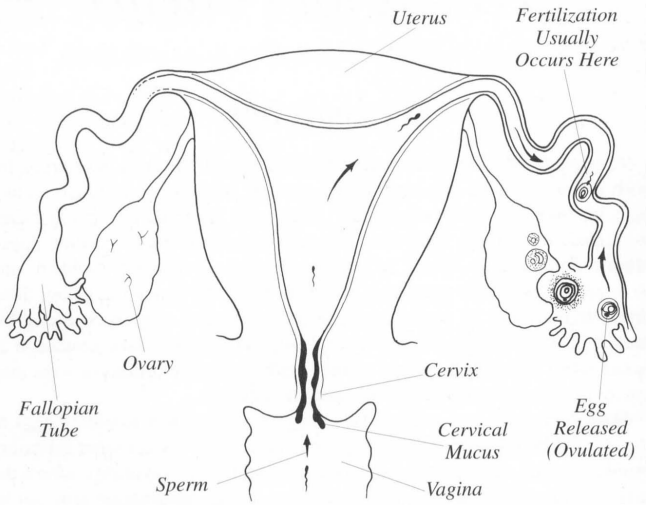
This booklet will help you understand *in vitro fertilization (IVF)* and other *assisted reproductive technologies (ART)* that have become accepted medical treatments for infertility. Through these procedures, many couples with otherwise untreatable infertility have given birth to healthy babies.

UNASSISTED REPRODUCTION

In order to understand assisted reproduction and how it can help infertile couples, it is important to understand how conception takes place naturally. For traditional conception to occur, the man must ejaculate his semen, the fluid containing the *sperm*, into the woman's *vagina* around the time of *ovulation*, when her *ovary* releases an egg. Ovulation is a complex event controlled by the *pituitary gland*, which is located at the base of the brain. The pituitary gland releases *follicle-stimulating hormone (FSH)*, which stimulates *follicles* in one of the ovaries to begin growing. The follicle produces the hormone *estrogen* and contains a maturing egg. When an egg is mature, the pituitary gland sends a surge of *luteinizing hormone (LH)* that causes the follicle to rupture and release (ovulate) a mature egg (Figure 1).

Following ovulation, the egg is picked up by one of the *fallopian tubes*. Since fertilization usually takes place inside the fallopian tube, the man's sperm must be capable of swimming through the vagina and *cervical mucus,* up the *cervical canal* into the *uterus*, and up into the fallopian tube, where it must penetrate the egg in order to fertilize it. The fertilized egg continues traveling to the uterus and implants in the uterine lining, where it continues to develop.

Figure 1



Solid arrows indicate path sperm must travel to reach the egg. Dotted arrow indicates path of egg. The fertilized egg continues traveling through the fallopian tube to the uterus.

IN VITRO FERTILIZATION (IVF)

There are many factors that can prevent the union of sperm and egg, and these are discussed in the ASRM patient information booklet titled, *Infertility, An Overview*. Fortunately, assisted reproductive technologies such as IVF can help. IVF is a method of assisted reproduction in which a man's sperm and a woman's eggs are combined outside of the body in a laboratory dish. One or more fertilized eggs (*embryos*) may be transferred into the woman's uterus, where they may implant in the uterine lining and develop. Excess embryos may be *cryopreserved* (frozen) for future use. Initially, IVF was used to treat women with blocked, damaged, or absent fallopian tubes. Today, IVF is used to treat many causes of infertility, such as *endometriosis* and *male factor*, or when a couple's infertility is unexplained. The basic steps in an IVF treatment cycle are *ovarian stimulation, egg retrieval, fertilization, embryo culture,* and *embryo transfer*. These are discussed in the following sections.

Ovarian Stimulation

During ovarian stimulation, also known as *ovulation induction*, medications or "fertility drugs," are used to stimulate multiple eggs to grow in the ovaries rather than the single egg that normally develops each month (Table 1) (Please see the ASRM booklet titled, *Medications for Inducing Ovulation* for more detailed information). Multiple eggs are stimulated because some eggs will not *fertilize* or develop normally after fertilization.

Table 1

Medications for Ovarian Stimulation

- human menopausal gonadotropin (hMG)
- follicle stimulating hormone (FSH)
- luteinizing hormone (LH) (used in conjunction with FSH)
- human chorionic gonadotropin (hCG)
- clomiphene citrate

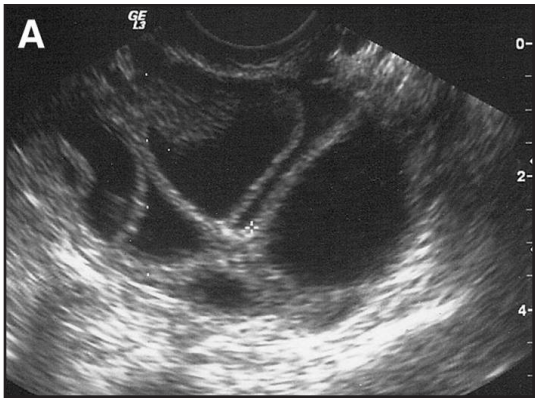
Medications to Prevent Premature Ovulation

- Gonadatropin releasing hormone (GnRH) agonists
- GnRH antagonists

Clomiphene citrate and letrozole are administered orally while the other medications listed are given by injection. These oral medications are less potent than injectable medications and are not as commonly used in ART cycles. There is no evidence that one injectable medication is superior to any other.

Timing is crucial in an IVF cycle. The ovaries are evaluated during treatment with vaginal *ultrasound* examinations to monitor the development of ovarian follicles (Figure 2). Blood samples are drawn to measure the response to ovarian stimulation medications. Normally, estrogen levels increase as the follicles develop, and *progesterone* levels are low until after ovulation.

Figure 2



Ovarian follicles, stimulated by ovulation medications, visible on ultrasound. The dark, circular areas are the follicles.

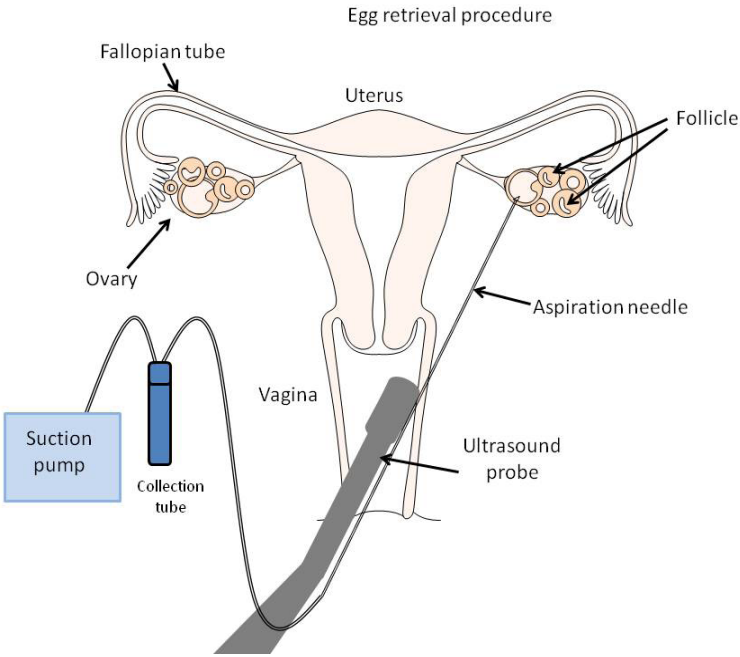
Using ultrasound examinations and blood testing, the physician can determine when the follicles are ready for egg retrieval. Generally, eight to 14 days of stimulation is required. When the follicles are ready, *hCG* or other medications are given. The hCG replaces the woman's natural LH surge and causes the final stage of egg maturation so the eggs are capable of being fertilized. The eggs are retrieved before ovulation occurs, usually 34 to 36 hours after the hCG injection is given.

Up to 20% of cycles may be cancelled prior to egg retrieval. IVF cycles may be cancelled for a variety of reasons, usually due to an inadequate number of follicles developing. Cancellation rates due to low response to the ovulation drugs increase with a woman's age, especially after age 35. When cycles are cancelled due to a poor response, alternate drug strategies may be helpful to promote a better response in a future attempt. Occasionally, a cycle may be cancelled to reduce the risk of *ovarian hyperstimulation syndrome (OHSS)*. Treatment with a *GnRH agonist* or *antagonist* reduces the possibility of premature LH surges from the pituitary gland, and thereby reduces the risk of premature ovulation. However, LH surges and ovulation occur prematurely in a small percentage of ART cycles despite the use of these drugs. When this occurs, since it is unknown when the LH surges began and eggs will mature, the cycle is usually cancelled. Collection of eggs from the peritoneal cavity after ovulation is not efficient.

Egg Retrieval

Egg retrieval is usually accomplished by *transvaginal ultrasound aspiration*, a minor surgical procedure that can be performed in the physician's office or an outpatient center. Some form of pain medication is generally administered. An ultrasound probe is inserted into the vagina to identify the follicles, and a needle is guided through the vagina and into the follicles (Figure 3).

Figure 3



Egg retrieval is usually performed through the vagina with an ultrasound-guided needle.

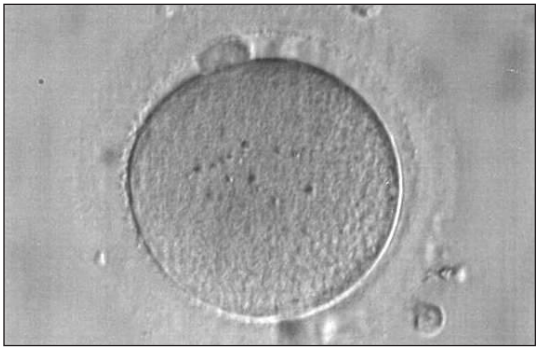
The eggs are aspirated (removed) from the follicles through the needle connected to a suction device. Removal of multiple eggs can usually be completed in less than 30 minutes. Some women experience cramping on the day of the retrieval, but this sensation usually subsides by the next day. Feelings of fullness and/or pressure may last for several weeks following the procedure because the ovaries remain enlarged. In some circumstances, one or both ovaries may not be accessible by transvaginal ultrasound.

Laparoscopy may then be used to retrieve the eggs using a small telescope placed in the umbilicus. For more information on laparoscopy, consult the ASRM patient information booklet titled, *Laparoscopy and Hysteroscopy*.

Fertilization and Embryo Culture

After the eggs are retrieved, they are examined in the laboratory for maturity and quality. Mature eggs (Figure 4) are placed in an *IVF culture medium* and transferred to an incubator to await fertilization by the sperm.

Figure 4



A mature, unfertilized egg.

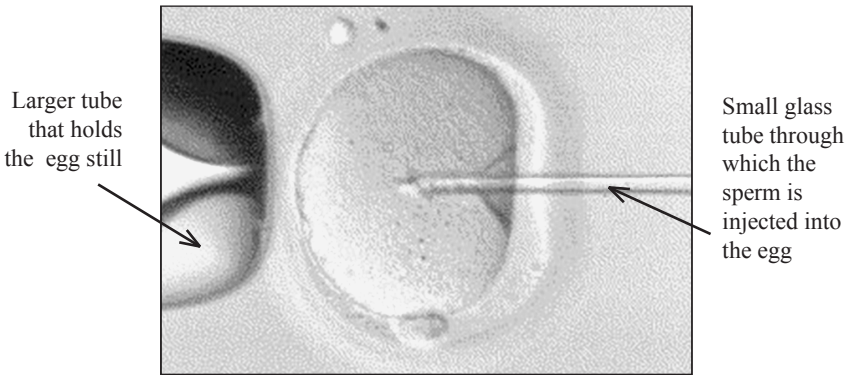
Sperm is separated from *semen* usually obtained by masturbation or in a special condom used during intercourse. Alternatively, sperm may be obtained from the testicle*, epididymis*, or *vas deferens* from men whose semen is void of sperm either due to an obstruction or lack of production.

Fertilization may be accomplished by *insemination*, where *motile* sperm are placed together with the oocytes and incubated overnight or by *intracytoplasmic sperm injection (ICSI)*, where a single sperm is directly injected into each mature egg (Figure 5). In the United States, ICSI is performed in approximately 60% of ART cycles. ICSI is usually performed when there is a likelihood of reduced fertilization, e.g., poor semen quality, history of failed fertilization in a prior IVF cycle. Overall, pregnancy and delivery rates with ICSI are similar to the rates seen with traditional IVF. Genetic counseling is advisable before ICSI if inherited abnormalities are identified that may be passed from father to son. For more information, see the ASRM fact sheet titled, *Intracytoplasmic*

Sperm Injection.

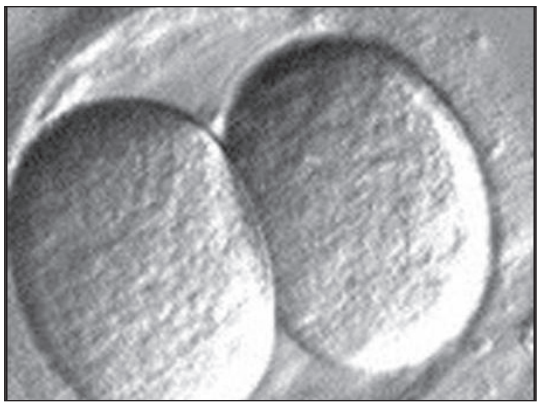
Visualization of two *pronuclei* the following day confirms fertilization of the egg. One pronucleus is derived from the egg and one from the sperm. Usually 65% to 75% of mature eggs will fertilize after insemination or ICSI. Lower rates may occur if the sperm and/or egg quality are poor. Occasionally, fertilization does not occur at all, even if ICSI was used. Two days after the egg retrieval, the fertilized egg has divided to become a 2- to 4-cell embryo (Figure 6).

Figure 5



Intracytoplasmic sperm injection (ICSI), in which a sperm is injected directly into an egg to facilitate fertilization.

Figure 6



A fertilized egg has divided once and is now a two-cell embryo.

By the third day, a normally developing embryo will contain approximately 6 to 10 cells. By the fifth day, a fluid cavity forms in the embryo, and the placenta and fetal tissues begin to separate. An embryo at this stage is called a *blastocyst*. Embryos may be transferred to the uterus at any time between one and six days after the egg retrieval. If successful development continues in the uterus, the embryo hatches from the surrounding *zona pellucida* and implants into the lining of the uterus approximately 6 to 10 days after the egg retrieval.

Assisted hatching (AH) is a *micromanipulation* procedure in which a hole is made in the zona pellucida just prior to embryo transfer to facilitate hatching of the embryo. Although AH has not been demonstrated definitively to improve live birth rates, AH may be used for older women or couples who have had unsuccessful prior IVF attempts. There is no clear benefit of AH to improve pregnancy or live birth rates in other groups of IVF patients. Please refer to the fact sheet on assisted hatching for more details.

Preimplantation genetic diagnosis (PGD) is performed at some centers to screen for inherited diseases. In PGD, one or two cells are removed from the developing embryo and tested for a specific genetic disease. Embryos that do not have the gene associated with the disease are selected for transfer to the uterus.

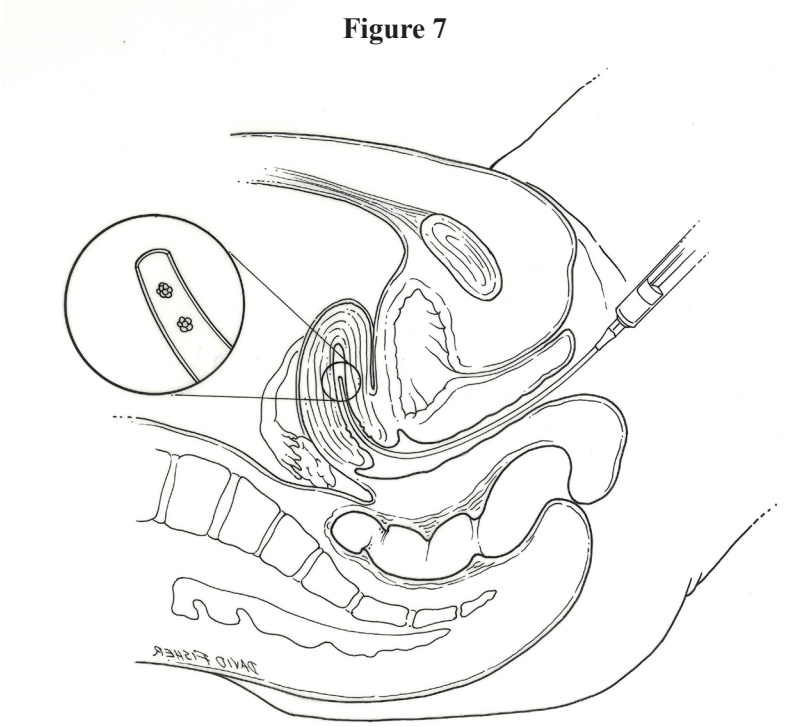
These procedures require specialized equipment and experience together with IVF (in a couple who may otherwise not need IVF to conceive). Some couples, especially those who are carriers of genetic diseases, consider embryo screening beneficial in reducing the risk of having an affected child. While PGD can reduce the likelihood of conceiving a pregnancy with an affected child, it cannot eliminate the risk. Confirmation with *chorionic villus sampling (CVS), amniocentesis* or other testing is still necessary.

Embryo Transfer

The next step in the IVF process is the embryo transfer. No anesthesia is necessary, although some women may wish to have a mild sedative. The physician identifies the cervix using a vaginal speculum. One or more embryos suspended in a drop of culture medium are drawn into a transfer catheter, a long, thin sterile tube with a syringe on one end. The physician gently guides the tip of the transfer catheter through the cervix and places

the fluid containing the embryos into the uterine cavity (Figure 7). The procedure is usually painless, although some women experience mild cramping. ASRM publishes guidelines regarding determination of how many embryos should be considered for transfer.

Figure 7



Embryo transfer is performed through the cervix.

The maximum number of embryos transferred is based on the patient's age and other individual patient and embryo characteristics. Since each embryo has a fair probability of implantation and development, the number of embryos to be transferred should be determined for each patient, taking into account the odds of achieving a pregnancy based on the number of embryos transferred weighed against the risk of *multiple gestation*. These guidelines have been effective in helping U.S. ART programs maintain their high success rates while significantly decreasing the number of high-order multiple pregnancies (triplets and higher). The reproductive endocrinologist or embryologist will discuss this with the patient prior to the transfer.

Cryopreservation

Extra embryos remaining after the embryo transfer may be cryopreserved (frozen) for future transfer. Cryopreservation makes future ART cycles simpler, less expensive, and less invasive than the initial IVF cycle, since the woman does not require ovarian stimulation or egg retrieval. Once frozen, embryos may be stored for prolonged periods, and live births have been reported using embryos that have been frozen for almost 20 years. However, not all embryos survive the freezing and thawing process, and the live birth rate is lower with cryopreserved embryo transfer. Couples should decide if they are going to cryopreserve extra embryos before undergoing IVF. There are two methods used to cryopreserve embryos: conventional (slow) freezing and "*vitrification*" or fast freezing. Your center will determine which method is best to use based on their experience and the developmental stage at which the embryos are frozen. Although some reports claim that vitrification may have higher success rates after thawing/warming, this is not the case at all centers.

It should also be noted that more and more ART centers are cryopreserving oocytes (eggs) prior to fertilization. This is done most commonly in young women who are about to undergo treatments or procedures that may affect their future fertility, such as chemotherapy for cancer. However, it is also used for couples who do not wish to freeze embryos because of concerns over their survival during freezing and thawing or the dilemma of what to do with remaining embryos after they have completed their families. Egg freezing is still considered experimental by the *Society for Assisted Reproductive Technology (SART),* although many clinics offer this procedure. Clinic success rates may vary.

Finally, it should be noted that although there are theoretical risks, freezing of sperm, eggs, and embryos is very safe. There have been no documented cases of infectious disease transmission, nor do the risks or birth defects, chromosomal anomalies, or pregnancy complications appear to be increased compared with using fresh sperm, eggs, or embryos.

VARIATIONS OF IVF

Gamete intrafallopian transfer (GIFT) is similar to IVF, but the gametes (egg and sperm) are transferred to the woman's fallopian tubes rather than her uterus, and fertilization takes place in the tubes rather than in

the lab. Another difference is that laparoscopy, a surgical procedure, is necessary to transfer the sperm and egg to the tubes. GIFT is an option only for women who have normal fallopian tubes. Some couples may consider GIFT for religious reasons because eggs are not fertilized outside the body. One limitation of GIFT is that fertilization cannot be confirmed as with IVF. Today, GIFT comprises less than 1% of ART procedures performed in the United States. Another ART procedure is *zygote intrafallopian transfer (ZIFT)*. This technique differs from GIFT in that fertilization takes place in the lab rather than the fallopian tube, but is similar in that the fertilized egg is transferred to the tube rather than the uterus. This procedure also requires a laparoscopy. Today, ZIFT comprises less than 1% of ART procedures performed in the United States.

SUCCESS RATES

The most recent rates for individual IVF programs in the United States are available on the Internet from the Society for Assisted Reproductive Technology (SART) at www.sart.org and from the *Centers for Disease Control and Prevention*: www.cdc.gov/art. Although this information is readily available, the results should be interpreted carefully. The success rates of an IVF center depend upon a number of factors, and a comparison of clinic success rates is not meaningful because patient characteristics and treatment approaches vary from clinic to clinic. For example, the type of patients accepted into the program and the numbers of embryos transferred per cycle affect the program's statistics. Statistics calculated on small numbers of cycles may not be accurate. An IVF center's rates may change dramatically over time, and the compiled statistics may not represent a program's current success.

It is also important to understand the definitions of pregnancy rates and live birth rates. For example, a pregnancy rate of 40% does not mean that 40% of women took babies home. Pregnancy does not always result in live birth. A *biochemical pregnancy* is a pregnancy confirmed by blood or urine tests but not visible on ultrasound, because the pregnancy stops developing before it is far enough along to be seen on ultrasound. A *clinical pregnancy* is one in which the pregnancy is seen with ultrasound, but stops developing sometime afterwards. Therefore, when comparing the "pregnancy" rates of different clinics, it is important to know which type of pregnancy is being compared. Most couples are more concerned with a clinic's live birth rate, which is the probability of delivering a live

baby per IVF cycle started. Pregnancy rates, and more importantly live birth rates, are influenced by a number of factors, especially the woman's age.

DONOR SPERM, EGGS, AND EMBRYOS

IVF may be performed with a couple's own eggs and sperm or with donor eggs, sperm, or both. A couple may choose to use a donor if there is a problem with their own sperm or eggs, or if they have a genetic disease that could be passed on to a child. Donors may be known or anonymous. In most cases, donor sperm is obtained from a sperm bank. Both sperm and egg donors undergo extensive medical and genetic screening, as well as testing for infectious diseases. Sexually transmitted disease screening and testing for both sperm and egg donation are highly regulated by the FDA.

Donor sperm is frozen and quarantined for six months, the donor is re-tested for infectious diseases including the AIDS virus, and sperm are only released for use if all tests are negative. Donor sperm may be used for *insemination* or in an ART cycle. Unlike intrauterine insemination (IUI) cycles, the use of frozen sperm in IVF cycles does not lower the chance of pregnancy.

Donor eggs are an option for women with a uterus who are unlikely or unable to conceive with their own eggs. Egg donors undergo much the same medical and genetic screening as sperm donors. Until recently, it has not been possible to freeze and quarantine eggs like sperm. Recent advances in oocyte freezing, though, have made this a possibility, and there are a few companies and clinics that are using such an approach. The egg donor may be chosen by the infertile couple or the ART program. Egg donors assume more risk and inconvenience than sperm donors. In the United States, egg donors selected by ART programs generally receive monetary compensation for their participation. Egg donation is more complex than sperm donation and is done as part of an IVF procedure. The egg donor must undergo ovarian stimulation and egg retrieval. During this time, the recipient (the woman who will receive the eggs after they are fertilized) receives hormonal medications to prepare her uterus for implantation. After the retrieval, the donor's eggs are fertilized by sperm from the recipient's partner and transferred to the recipient's uterus. The recipient will not be genetically related to the child, but she is a biologic parent in the sense that she will carry

the pregnancy and give birth. Egg donation is expensive because donor selection, screening, and treatment add additional costs to the IVF procedure. However, the relatively high live birth rate for egg donation, over 50% nationally, provides many couples with their best chance for success. Overall, donor eggs are used in nearly 10% of all ART cycles in the United States.

In some cases, when both the man and woman are infertile, both donor sperm and eggs have been used. Donor embryos may also be used in these cases. Some IVF programs allow couples to donate their unused frozen embryos to other infertile couples. Appropriate screening of the individuals whose genetic embryos are used should adhere to federal and state guidelines. The use of donor sperm, eggs, or embryos is a complicated issue that has lifelong implications. Talking with a trained counselor who understands donor issues can be very helpful in the decision-making process. Many programs have a mental health professional on staff or the physician may recommend one. If a couple knows the donor, their physician may suggest that both the couple and the donor speak with a counselor and an attorney. Some states require and most IVF centers recommend an attorney to file paperwork for the couple with the court when donor gametes or embryos are used.

SURROGACY/GESTATIONAL CARRIER

A pregnancy may be carried by the egg donor (*traditional surrogate*) or by another woman who has no genetic relationship to the baby (*gestational carrier*). If the embryo is to be carried by a surrogate, pregnancy may be achieved through insemination alone or through ART. The surrogate will be biologically related to the child. If the embryo is to be carried by a gestational carrier, the eggs are removed from the infertile woman, fertilized with her partner's sperm, and transferred into the gestational carrier's uterus. The gestational carrier will not be genetically related to the child. All parties benefit from psychological and legal counseling before pursuing surrogacy or a gestational carrier.

RISKS OF ART

The medical risks of ART depend upon each specific step of the procedure. The following are some of the primary risks of ART procedures:

Ovarian stimulation carries a risk of hyperstimulation, where the ovaries become swollen and painful. Fluid may accumulate in the abdominal cavity and chest, and the woman may feel bloated, nauseated, and experience vomiting or lack of appetite. Up to 30% of woman undergoing ovarian stimulation have a mild case of ovarian hyperstimulation syndrome (OHSS) that can be managed with over-the-counter painkillers and a reduction in activity. In moderate OHSS, women develop or accumulate fluid within the abdominal cavity, and gastrointestinal symptoms may occur. These women are monitored closely, but generally do very well with simple outpatient management. The condition tends to resolve without intervention unless pregnancy occurs, in which case recovery may be delayed for several weeks. Up to 2% of women develop severe OHSS characterized by excessive weight gain, fluid accumulation in the abdomen and chest, electrolyte abnormalities, over-concentration of the blood, and, in rare cases, the development of blood clots, kidney failure, or death. It may be medically necessary to drain fluid from the abdomen with a needle if breathing becomes difficult. Women with severe OHSS require hospitalization until the symptoms improve. If pregnancy occurs, OHSS can worsen. Occasionally, termination of pregnancy must be considered in the most severe cases.

Although initial reports suggested that women who use fertility drugs have an increased risk for ovarian cancer, numerous recent studies support the conclusion that fertility drugs are not linked to ovarian cancer. Nevertheless, there is still uncertainty whether a risk exists, and research continues to address this question. An annual gynecologic visit is recommended for all women with examination of the ovaries, regardless of prior use of ovulation medications.

There are risks related to the egg retrieval procedure. Laparoscopy carries the risks of any surgery that requires anesthesia. Removing eggs through an aspirating needle entails a slight risk of bleeding, infection, and damage to the bowel, bladder, or a blood vessel. This is true whether the physician uses laparoscopy or ultrasound to guide the needle. Less than one patient in 1,000 will require major surgery to repair damage from complications of the egg retrieval procedure. In rare cases, infection may occur from the retrieval or embryo transfer.

The chance of multiple pregnancy is increased in all assisted reproductive technologies when more than one embryo is transferred. Although some would consider twins a happy result, there are many problems associated with multiple births, and problems become progressively more severe and common with triplets and each additional fetus thereafter. Women carrying a multiple pregnancy may need to spend weeks or even months in bed or in the hospital in an attempt to delay preterm delivery. The risk of preterm delivery in multiple pregnancies is high, and babies may be born too early to survive. Premature babies require prolonged and intensive care and risk lifelong handicaps due to premature birth. Some couples may consider *multifetal pregnancy reduction* to decrease the risks due to multiple pregnancy, but this is likely to be a difficult decision. For more information on this topic, refer to the ASRM patient information booklet titled *Multiple Pregnancy and Birth: Twins, Triplets and Higher Order Multiples* and the ASRM patient fact sheet, *Complications and Problems Associated with Multiple Birth*. Data also suggest that IVF conceptions, even singletons, have a slightly increased risk of preterm delivery or low birth weight.

First trimester bleeding may signal a possible miscarriage or *ectopic pregnancy*. If bleeding or pain (before 13 weeks) occurs, a medical evaluation is needed to determine the cause. Some evidence suggests that early bleeding is more common in women who undergo IVF and GIFT and is not associated with the same poor prognosis as it is in women who conceive spontaneously.

Miscarriage may occur after ART, even after ultrasound identifies a pregnancy in the uterus. Miscarriage occurs after ultrasound in nearly 15% of women younger than age 35, in 25% at age 40, and in 35% at age 42 following ART procedures. In addition, there is approximately a 5% chance of ectopic pregnancy with ART. It is not clear whether the risk of birth defects is increased with IVF. Most studies do not show an increased risk, but several studies do. Research is ongoing to determine the magnitude, if any, of this risk. Furthermore, when ICSI is used in cases of severe male factor infertility, a genetic cause of male infertility may be passed on to the offspring.

Assisted reproductive technologies involve significant physical, financial, and emotional commitments on the part of the couple. Psychological

stress is common, and some couples describe the experience as an emotional roller coaster. The treatments are involved and costly. Patients have high expectations, yet failure is common in any given cycle. Couples may feel frustrated, angry, isolated, and resentful. At times, frustration can lead to depression and feelings of low self-esteem, especially in the immediate period following a failed ART attempt. The support of friends and family members is very important at this time. Couples are encouraged to consider psychological counseling as an additional means of support and stress management. Many ART programs have a mental health professional on staff to help couples deal with the grief, tension, or anxieties associated with infertility and its treatment.

PREPARATION FOR ART

Preliminary preparation for an ART procedure may be as important as the procedure itself. Testing for *ovarian reserve* may be recommended in order to predict how the ovaries will respond to fertility medication. The chance of success may be poor, for example, if tests demonstrate diminished ovarian reserve or fertility potential. Ovarian reserve may be determined by any of these methods: measuring FSH and *estradiol* levels on the second or third day of a menstrual cycle, measuring the level of *AMH (anti-müllerian hormone)*, performing a *clomiphene citrate challenge test,* or counting the number of small follicles in the ovary (*antral follicle count*). An elevated FSH and/or estradiol level, a low antral follicle count, or a low AMH level is associated with reduced pregnancy rates, especially in women over the age of 35 years. However, age itself is the single most important factor in determining the chances for success with IVF.

Uterine cavity abnormalities such as *fibroids*, *polyps*, or a *septum* may need to be corrected before IVF or GIFT. A *hydrosalpinx*, a fluid filled, blocked fallopian tube, reduces IVF success. Some physicians advise clipping or removing the affected tube prior to IVF. For more information, see the ASRM patient fact sheet titled, *Hydrosalpinx*.

Semen is tested before ART. If semen abnormalities are identified, consultation with a specialist in male infertility should determine if there are correctable problems or underlying health concerns. For example, genetic abnormalities in the Y chromosome have been linked to some

cases of male infertility; and men born without a vas deferens, the tube that transports sperm from the testicle, are often carriers of a gene that causes cystic fibrosis. In these circumstances, genetic testing may be advisable. Major advances have been made in the treatment of male infertility, and IVF may help some men who were previously considered sterile. Detailed consultation with a specialist in male infertility is essential.

When sperm cannot be collected by masturbation, other forms of sperm retrieval are available. For example, for men who cannot *ejaculate*, such as those with spinal cord injuries, medical procedures to assist ejaculation are recommended. These procedures include *penile vibratory stimulation (PVS)* and *electroejaculation (EEJ)*. During PVS, a strong vibrator is placed on the head of the penis to deliver stimulation resulting in ejaculation. During EEJ, electrical impulses from a probe placed in the rectum near the prostate often stimulate ejaculation. For men who are able to ejaculate, but who do not produce sperm in their semen, medical procedures are available to retrieve sperm from reproductive tissues. These procedures include *microepididymal sperm aspiration (MESA)*, *percutaneous epididymal sperm aspiration (PESA)*, or *testicular sperm extraction (TESE)*. MESA can be performed to recover sperm after *vasectomy* or after failed vasectomy reversal, and in some men with absence of the vas deferens. TESE involves testicular biopsy and recovery of sperm directly from testicular tissue, and may be performed in an office setting with local anesthesia. Sperm obtained by these methods may be frozen, stored, and thawed for later ART.

Lifestyle issues should be addressed before ART. Smoking, for example, may lower a woman's chance of success by as much as 50%. Live birth rates after ART decrease significantly with obesity, due to a combination of lower pregnancy rates and higher miscarriage rates. Achieving a more optimal weight prior to undergoing IVF appears to be appropriate. All medications, including over-the-counter supplements, should be reviewed since some may have detrimental effects. Alcohol and recreational drugs may be harmful, and excessive caffeine consumption should be avoided. Because folic acid taken prior to pregnancy reduces the risk of neural tube defects such as *spina bifida*, women should take prenatal vitamins containing at least 400 micrograms of folic acid before beginning an ART cycle. A complete exam and Pap smear may identify problems that should be treated before pregnancy.

A detailed examination of ART insurance benefits is helpful. Even if ART is excluded from a policy, coverage may be available for some aspects of these procedures. Couples should consult their company's benefits director in advance, since options such as a medical savings account may be available. It is also important to determine the costs for the ART treatment cycle. Keep in mind that fees for initial consultation, screening tests, medications, and special procedures such as ICSI and cryopreservation may not be included in the estimate. Other expenses to consider include travel, lodging, and time missed from work.

SELECTING AN ART PROGRAM

When selecting an ART program, information is crucial. Important points for consideration include the qualifications and experience of personnel, types of patients being treated, support services available, cost, convenience, live birth rates per ART cycle started, and multiple pregnancy rates. Older programs have established live birth rates based on years of experience. Small and new programs may still be determining their live birth rates, although their personnel may be equally well qualified. Every couple wants to use the most successful ART program, but many factors contribute to the overall success of a program. For example, some clinics may be willing to accept patients with a low chance of success. A clinic may specialize in certain types of infertility treatment. Costs may vary among programs. A couple may prefer a program based on interpersonal interactions with the ART team, or may feel more confident in the recommended treatment plan. Consequently, it is not appropriate to compare programs based only on the published pregnancy rates.

Credibility is important too. Does the program adhere to the guidelines set forth by the American Society for Reproductive Medicine (ASRM)? Is the program a member of SART, a society affiliated with the ASRM? Is the IVF lab accredited by the College of American Pathologists or by the Joint Commission? These organizations require ART programs to have personnel on their staff that have been trained in reproductive endocrinology, laparoscopic surgery, sonography, hormone measurement, tissue culture technique, and sperm/egg interaction. Are the physicians board certified in reproductive endocrinology and infertility? Does the program report its results to SART/CDC? The compiled results are published in *Fertility and Sterility*, the ASRM journal, and results are available on the SART Web site at www.sart.org and the CDC's Web

site at: www.cdc.gov/art. The above considerations and answers to the following questions, which may be asked of each program, will help you make an informed decision when choosing an ART program.

Cost and Convenience

- What pre-cycle screening tests are required, how much do they cost, and will my insurance provide coverage for these tests?
- How much does the ART procedure cost, including drugs per treatment cycle?
- Do I pay in advance? How much? What are the methods of payment?
- If applicable, will you submit any bills to my insurance company? How much do I pay if my treatment cycle is canceled before egg recovery? Before embryo transfer?
- What are the costs for embryo freezing, storage, and transfer?
- How much work will I miss? How much will my partner miss?
- Do you help arrange (low-cost) lodging, if needed?

Details about the Program

- Is the program a member of the Society for Assisted Reproductive Technology (SART)?
- Does the program meet and follow ASRM/SART guidelines?
- Does the program report its results to SART/CDC?
- How many physicians will be involved in my care?
- Are one or more physicians board certified in reproductive endocrinology?
- To what degree can my own physician participate in my care?
- What types of counseling and support services are available?
- Whom do I call day or night if I have a problem?
- Do you freeze embryos (cryopreservation)?
- Is donor sperm available in your program? Donor eggs? Donor embryos?
- Do you have an age or basal FSH cut-off?
- Do you perform ICSI? If so, when? What is the cost?
- Do you perform assisted hatching? If so, when? What is the cost?
- How many eggs/embryos would be transferred in my case?
- Who makes the final decision to cancel the cycle if my response to stimulation is sub-optimal?

Success of the Program

SART is a very good source of information from which to obtain ART outcomes for each member program in the United States. This information may be a year old, so it is important to find out if there have

been any significant changes in the program since the most recent report, including:

- Personnel changes
- Changes in the approach to ovarian stimulation, egg retrieval, embryo culture, or embryo transfer
- Change in the number of cycles
- Change in the miscarriage rate, live birth rate per cycle started, or the multiple pregnancy rate

If a program cites a live birth rate for each procedure, be sure that the program representative counts twins as one successful pregnancy, not two. When discussing recent ART program outcomes, keep in mind that the live birth rate may vary depending on the denominator used - i.e., per cycle started, per retrieval, or per embryo transfer. For example, live birth rates per egg retrieval do not consider cancelled cycles, and rates based per embryo transfer do not include cancelled cycles or fertilization failures. Therefore, live birth rates per cycle are higher per egg retrieval and are highest per embryo transfer.

WHEN TO END TREATMENT

Studies indicate that the chance for pregnancy in consecutive IVF cycles remains similar in up to four cycles. However, many other factors should be considered when determining the appropriate endpoint in therapy, including financial and psychological reserves. Members of the IVF team can help couples decide when to stop treatment and discuss other options such as egg and/or sperm donation or adoption, if appropriate. The physician, support groups, and other couples undergoing infertility treatment can provide valuable support and guidance.

CONCLUSION

The decision to seek treatment for infertility is a viable one due to the assisted reproductive technologies available today. With patience, a positive attitude, and the appropriate treatment, most infertile couples will eventually experience the joys of parenthood. For additional information, visit www.sart.org and www.cdc.gov/art.

For more information on this and other reproductive health topics visit www.ReproductiveFacts.org

Let Us Know What You Think
Email your comments on this booklet to asrm@asrm.org.
In the subject line, type "Attention: Patient Education Committee"

GLOSSARY

American Society for Reproductive Medicine (ASRM). A professional medical organization of more than 8,000 health care professionals dedicated to reproductive medicine.

Amniocentesis. A procedure in which a small amount of amniotic fluid is removed through a needle from the fetal sac at about 16 weeks into a pregnancy. The fluid is studied for chromosomal or other abnormalities which may affect fetal development.

Anti-müllerian Hormone (AMH). A hormone which is often measured in a woman to help determine her egg supply, or "ovarian reserve". It is secreted by small, growing follicles.

Antral follicle count. The number of follicles noted by ultrasound at the beginning of the menstrual cycle, usually day 2 or 3.

Assisted hatching (AH). A procedure in which the zona pellucida (outer covering) of the embryo is partially opened, usually by application of an acid or laser, to facilitate embryo implantation and pregnancy.

Assisted reproductive technologies (ART). All treatments which include the handling of eggs and/or embryos. Some examples of ART are in vitro fertilization (IVF), gamete intrafallopian transfer (GIFT), pronuclear stage tubal transfer (PROST), tubal embryo transfer (TET), and zygote intrafallopian transfer (ZIFT).

Biochemical pregnancy. When a woman's pregnancy test is initially positive but becomes negative before a gestational sac is visible on ultrasound.

Blastocyst. An embryo that has formed a fluid-filled cavity and the cells have begun to form the early placenta and embryo, usually 5 days after ovulation or egg retrieval.

Centers for Disease Control and Prevention. Federal agency for protecting the health and safety of people at home and abroad, providing credible information to enhance health decisions, and promoting health through strong partnerships.

Cervical canal. The passageway leading from the vagina into the uterus.

Cervical mucus. The substance in the cervix through which sperm must swim to enter the uterus.

Cervix. The narrow, lower end of the uterus.

Clinical pregnancy. A pregnancy confirmed by an increasing level of hCG and the presence of a gestational sac detected by ultrasound.

Clomiphene citrate challenge test (CCCT). A test of ovarian reserve in which serum FSH is checked on days three and ten of the menstrual cycle and clomiphene citrate is taken on days five through nine.

Clomiphene citrate. An oral antiestrogen medication used to induce ovulation.
Cryopreservation. Freezing at a very low temperature, such as in liquid nitrogen (-196°C) to keep embryos, eggs, or sperm viable.
Cryopreserved. Frozen.
Ectopic pregnancy. A pregnancy in the fallopian tube or elsewhere outside the lining of the uterus.
Egg (oocyte). The female sex cell (ovum) produced by the ovary, which, when fertilized by a male's sperm, produces an embryo.
Egg retrieval. The procedure in which eggs are obtained by inserting a needle into the ovarian follicle and removing the fluid and the egg by suction. Also called oocyte aspiration.
Electroejaculation (EEJ). Procedure to cause ejaculation of sperm, performed by electrical stimulation of tissue in the region of the prostate.
Embryo. A fertilized egg that has begun cell division.
Embryo culture. Growth of the embryo in a laboratory (culture) dish.
Embryo transfer. Placement of an embryo into the uterus or, in the case of ZIFT and TET, into the fallopian tube.
Endometriosis. A disease in which tissue resembling endometrium (the lining of the uterus) grows outside the uterus. It is often associated with infertility.
Epididymis. The duct between testes and vas deferens where sperm are stored and mature.
Estradiol. The predominant estrogen (hormone) produced by the follicular cells of the ovary.
Estrogen. The female hormone largely responsible for thickening the uterine lining during the first half of the menstrual cycle in preparation for ovulation and possible pregnancy. Estradiol is the main estrogen.
Fallopian tubes. A pair of tubes attached to the uterus, one on each side, where sperm and egg meet in normal conception.
Fertilization. The fusion of sperm and egg.
Fibroids. Benign (non-cancerous) tumors of the uterine muscle wall that can cause abnormal uterine bleeding and pain.
Follicle. A fluid-filled structure in the ovary containing an egg and the surrounding cells that produce hormones. As the follicle matures, the fluid can be visualized by ultrasound.
Follicle-stimulating hormone (FSH). The pituitary hormone responsible for stimulating the growth of the follicle that surrounds the egg. In addition, it is the hormone in injectable ovulation medications that promotes growth of the follicles.

Gamete intrafallopian transfer (GIFT). The direct transfer of sperm and eggs into the fallopian tube. Fertilization takes place inside the tube.
Gestational carrier. A woman who carries a pregnancy for another couple. The pregnancy is derived from the egg and sperm of the couple. Although she carries the pregnancy to term, she does not have a genetic relationship to the resulting child.
Gonadotropin releasing hormone (GnRH). Hormone secreted by the hypothalamus, a control center in the brain, which prompts the pituitary gland to release FSH and LH into the bloodstream.
GnRH agonists. A GnRH analog that initially stimulates the pituitary gland to release LH and FSH, followed by a delayed suppressive effect. GnRH agonists are also used to help stimulate follicle growth when started at the beginning of an IVF cycle.
GnRH analogs. Synthetic hormones similar to the naturally occurring gonadotropin releasing hormone used to prevent premature ovulation. There are two types of GnRH analogs: GnRH agonists and GnRH antagonists.
GnRH antagonists. Synthetic hormones similar to the naturally occurring gonadotropin releasing hormone used to prevent premature ovulation. These medications have an immediate suppressive effect on the pituitary gland.
Human chorionic gonadotropin (hCG). A hormone produced by the placenta; its detection is the basis for most pregnancy tests. Also refers to the medication used to induce ovulation and during the final stages of egg maturation.
Human menopausal gonadotropin (hMG). An ovulation drug that contains follicle stimulating hormone (FSH) and luteinizing hormone (LH) derived from the urine of postmenopausal women. hMG is used to stimulate the growth of multiple follicles.
Hydrosalpinx. A blocked, dilated, fluid-filled fallopian tube.
Intracytoplasmic sperm injection (ICSI). A micromanipulation procedure in which a single sperm is injected directly into an egg to attempt fertilization, used with male infertility or couples with prior IVF fertilization failure.
Insemination. Placement of sperm into the uterus or cervix for producing a pregnancy, or adding sperm to eggs in IVF procedures.
In vitro fertilization (IVF). A process in which an egg and sperm are combined in a laboratory dish to facilitate fertilization. If fertilized, the resulting embryo is transferred to the uterus.

IVF culture medium. A special fluid into which sperm, eggs, and embryos are placed when outside the human body.
Laparoscopy. A surgical procedure that allows viewing of the internal pelvic organs. During the procedure, a long, narrow, fiber optic instrument, called a laparoscope, is usually inserted through an incision in or below the woman's navel. One or more additional incisions may be made for inserting additional instruments.
Luteinizing hormone (LH). The pituitary hormone that normally causes ovulation and maturation of the egg.
Male factor. Infertility caused by a problem in the male; for example the inability to ejaculate or insufficient number of sperm.
Microepididymal sperm aspiration (MESA). Outpatient microsurgical procedure used to collect sperm in men with blockage of the male reproductive ducts such as prior vasectomy or absence of the vas deferens. Used in IVF-ICSI procedures.
Micromanipulation. The IVF laboratory process whereby the egg or embryo is held with special instruments and surgically altered by procedures such as intracytoplasmic sperm injection (ICSI), assisted hatching, or embryo biopsy.
Motile. Moving.
Multifetal pregnancy reduction. Also known as selective reduction. A procedure to reduce the number of fetuses in the uterus. This procedure is sometimes performed on women who are pregnant with multiple fetuses who are at an increased risk of late miscarriage or premature labor. These risks increase with the number of fetuses.
Oocyte. Medical term for egg, the female gamete. Also called ovum (singular) or ova (plural).
Ovarian hyperstimulation syndrome (OHSS). A condition that may result from ovulation induction characterized by enlargement of the ovaries, fluid retention, and weight gain.
Ovarian reserve. A woman's fertility potential in the absence of specific pathophysiologic changes in her reproductive system. Diminished ovarian reserve is associated with depletion in the number of eggs and worsening of oocyte quality.
Ovarian stimulation. See Ovulation induction.
Ovary (Ovaries). The two female sex glands in the pelvis, located one on each side of the uterus. The ovaries produce eggs and hormones including estrogen, progesterone, and androgens.
Ovulation. Release of an egg from the ovary.

Ovulation induction. The administration of hormone medications (ovulation drugs) that stimulate the ovaries to produce multiple eggs. Sometimes called enhanced follicular recruitment or controlled ovarian hyperstimulation.

Penile vibratory stimulation (PVS). A procedure to cause ejaculation of sperm, performed by vibratory stimulation of the penis.

Percutaneous epididymal sperm aspiration (PESA). A sperm aspiration procedure in which a needle is inserted into the epididymis (gland that carries sperm from testicle to vas deferens) in order to retrieve sperm for use in an IVF procedure.

Pituitary gland. A small gland just beneath the hypothalamus in the brain that secretes follicle stimulating hormone (FSH) and luteinizing hormone (LH).

Polyps. A general term that describes any mass of tissue which bulges or projects out or upward from the normal surface level.

Preimplantation genetic diagnosis (PGD). A test performed by an embryologist in which one or two cells are removed from an embryo. The removed cells are then screened for genetic abnormalities. PGD may be performed in conjunction with IVF.

Progesterone. A female hormone secreted during the second half of the menstrual cycle. It prepares the lining of the uterus for implantation of a fertilized egg.

Pronuclei. The nuclei of the male and female gametes (sperm and egg) seen in the one-cell embryo (zygote).

Septum, uterine. A band of fibrous tissue present from birth that forms a wall within the uterine cavity. A septum may increase the risk of miscarriage and other pregnancy complications.

Semen. The fluid ejaculated by the male.

Society for Assisted Reproductive Technology (SART). A society affiliated with the ASRM and comprised of representatives from assisted reproductive technology programs who have demonstrated their ability to perform IVF.

Sperm. The male reproductive cells that fertilize a woman's egg. The sperm head carries genetic material (chromosomes), the midpiece produces energy for movement, and the long, thin tail wiggles to propel the sperm.

Sperm preparation. A method of treating semen to remove the seminal fluid and isolate the sperm cells.

Spina bifida. A birth defect of the spinal column. Spina bifida is the failure of the spine to close properly during development.

Testicular sperm extraction (TESE). Operative removal of testicular tissue in an attempt to collect living sperm for use in an IVF-ICSI procedure.

Traditional surrogate. A woman who carries a pregnancy intended for an infertile couple. The surrogate's egg is fertilized with sperm from the male partner of the infertile couple.

Transvaginal ultrasound aspiration. An ultrasound-guided technique for egg retrieval whereby a long, thin needle is passed through the vagina into the ovarian follicle and suction is applied to accomplish retrieval.

Ultrasound. A technology that uses high-frequency sound waves to form an image of internal organs on a monitor screen; used by fertility specialists to monitor the growth of ovarian follicles and to retrieve the eggs from the follicles and evaluate a pregnancy.

Uterus (womb). The hollow, muscular female reproductive organ in the pelvis in which an embryo implants and grows during pregnancy. The lining of the uterus, called the endometrium, produces the monthly menstrual blood flow when there is no pregnancy.

Vagina. The canal in the female that leads to the cervix, which leads to the uterus.

Vas deferens. The two muscular tubes that carry sperm from the epididymis to the urethra.

Vitrification. An ultra-rapid method of freezing eggs and embryos that may offer certain advantages compared to traditional types of cryopreservation.

Zona pellucida. The egg's outer layer that a sperm must penetrate in order to fertilize the egg.

Zygote. A fertilized egg before cell division (cleavage) begins.

Zygote intrafallopian tube transfer (ZIFT). An egg is fertilized in the laboratory and the zygote is transferred to the fallopian tube before cell division takes place. Eggs are retrieved and fertilized on one day and the embryo is transferred the following day.

Notes

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