

Age and Fertility

A Guide for Patients



PATIENT INFORMATION SERIES

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

INTRODUCTION

Fertility changes with age. Both males and females become fertile in their teens following puberty. For girls, the beginning of their reproductive years is marked by the onset of ovulation and menstruation. It is commonly understood that after *menopause* women are no longer able to become pregnant. Generally, reproductive potential decreases as women get older, and fertility can be expected to end 5 to 10 years before menopause.

In today's society, age-related *infertility* is becoming more common because, for a variety of reasons, many women wait until their 30s to begin their families. Even though women today are healthier and taking better care of themselves than ever before, improved health in later life does not offset the natural age-related decline in fertility. It is important to understand that fertility declines as a woman ages due to the normal age-related decrease in the number of *eggs* that remain in her *ovaries*. This decline may take place much sooner than most women expect.

OVULATION AND THE MENSTRUAL CYCLE

During their reproductive years, women have regular monthly menstrual periods because they ovulate regularly each month. Eggs mature inside of fluid-filled spheres called "*follicles*." At the beginning of each menstrual cycle when a woman is having her period, a *hormone* produced in the *pituitary gland*, which is located in the brain, stimulates a group of follicles to grow more rapidly on both ovaries. The pituitary hormone that stimulates the ovaries is called *follicle-stimulating hormone (FSH)*. Normally, only one of those follicles will reach maturity and release an egg (*ovulate*); the remainder gradually will stop growing and degenerate. Pregnancy results if the egg becomes fertilized and implants in the lining of the uterus (*endometrium*). If pregnancy does not occur, the endometrium is shed as the menstrual flow and the cycle begins again. In their early teens, girls often have irregular *ovulation* resulting in irregular menstrual

cycles, but by age 16 they should have established regular ovulation resulting in regular periods. A woman's cycles will remain regular, 26 to 35 days, until her late 30s to early 40s when she may notice that her cycles become shorter. As time passes, she will begin to skip ovulation resulting in missed periods. Ultimately, periods become increasingly infrequent until they cease completely. When a woman has not had a menstrual period for 1 full year, she is said to be in menopause.

As women age, fertility declines due to normal, age-related changes that occur in the ovaries. Unlike men, who continue to produce *sperm* throughout their lives, a woman is born with all the egg-containing follicles in her ovaries that she will ever have. At birth there are about one million follicles. By puberty that number will have dropped to about 300,000. Of the follicles remaining at puberty, only about 300 will be ovulated during the reproductive years. The majority of follicles are not used up by ovulation, but through an ongoing gradual process of loss called *atresia*. Atresia is a degenerative process that occurs regardless of whether you are pregnant, have normal menstrual cycles, use birth control, or are undergoing infertility treatment. Smokers appear to experience menopause about 1 year earlier than non-smokers.

FERTILITY IN THE AGING FEMALE

A woman's best reproductive years are in her 20s. Fertility gradually declines in the 30s, particularly after age 35. Each month that she tries, a healthy, fertile 30-year-old woman has a 20% chance of getting pregnant. That means that for every 100 fertile 30-year-old women trying to get pregnant in 1 cycle, 20 will be successful and the other 80 will have to try again. By age 40, a woman's chance is less than 5% per cycle, so fewer than 5 out of every 100 women are expected to be successful each month.

Women do not remain fertile until menopause. The average age for menopause is 51, but most women become unable to have a successful pregnancy sometime in their mid-40s. These percentages are true for natural conception as well as conception using fertility treatment, including *in vitro* fertilization (IVF). Although stories in the news media may lead women and their partners to believe that they will be able to use fertility treatments such as IVF to get pregnant, a woman's age affects the success rates of infertility treatments. The age-related loss of female fertility happens because both the quality and the quantity of eggs gradually decline.

FERTILITY IN THE AGING MALE

Unlike the early fertility decline seen in women, a man's decrease in sperm characteristics occurs much later. Sperm quality deteriorates somewhat as men get older, but it generally does not become a problem before a man is in his 60s. Though not as abrupt or noticeable as the changes in women, changes in fertility and sexual functioning do occur in men as they grow older. Despite these changes, there is no maximum age at which a man cannot father a child, as evidenced by men in their 60s and 70s conceiving with younger partners. As men age, their *testes* tend to get smaller and softer, and sperm *morphology* (shape) and *motility* (movement) tend to decline. In addition, there is a slightly higher risk of gene defects in their sperm. Aging men may develop medical illnesses that adversely affect their sexual and reproductive function. Not all men experience significant changes in reproductive or sexual functioning as they age, especially men who maintain good health over the years. If a man does have problems with *libido* or erections, he should seek treatment through his primary care provider and/or urologist. Decreased libido may be related to low levels of *testosterone*.

EGG QUALITY

Women become less likely to become pregnant and more likely to have *miscarriages* because egg quality decreases as the number of remaining eggs dwindle in number. These changes are most noted as she reaches her mid-to-late 30s. Therefore, a woman's age is the most accurate test of egg quality. An important change in egg quality is the frequency of *genetic* abnormalities called aneuploidy (too many or too few *chromosomes* in the egg). At fertilization, a normal egg should have 23 chromosomes, so that when it is fertilized by a sperm also having 23 chromosomes, the resulting embryo will have the normal total of 46 chromosomes. As a woman gets older, more and more of her eggs have either too few or too many chromosomes. That means that if fertilization occurs, the embryo also will have too many or too few chromosomes. Most people are familiar with *Down syndrome*, a condition that results when the embryo has an extra chromosome 21. Most embryos with too many or too few chromosomes do not result in pregnancy at all or result in miscarriage. This helps explain the lower chance of pregnancy and higher chance of miscarriage in older women.

EGG QUANTITY

The decreasing quantity of egg-containing follicles in the ovaries is called “loss of *ovarian reserve*.” Women begin to lose ovarian reserve before they become infertile and before they stop having regular periods. Since women are born with all of the follicles they will ever have, the pool of waiting follicles is gradually used up. As ovarian reserve declines, the follicles become less and less sensitive to FSH stimulation, so that they require more stimulation for an egg to mature and ovulate. At first, periods may come closer together resulting in short cycles, 21 to 25 days apart. Eventually, the follicles become unable to respond well enough to consistently ovulate, resulting in long, irregular cycles. Diminished ovarian reserve is usually age-related and occurs due to the natural loss of eggs and decrease in the average quality of the eggs that remain. However, young women may have reduced ovarian reserve due to smoking, family history of premature menopause, and prior ovarian surgery. Young women may have diminished ovarian reserve even if they have no known risk factors.

There are medical tests for ovarian reserve, but none have been proven to reliably predict the possibility of becoming pregnant. These tests do not determine whether or not a woman can become pregnant, but they can determine that age-related changes of the ovaries have begun. Women with poor ovarian reserve have a lower chance of becoming pregnant than women with normal ovarian reserve in their same age group. No single test nor any combination of tests is 100% accurate. Tests of day-3 FSH, antimüllerian hormone, and *estrogen* levels involve blood sampling on the 2nd, 3rd, or 4th day of the menstrual cycle. High levels of FSH or estrogen indicate that ovarian reserve is low. However, many women with diminished ovarian reserve will have normal levels of FSH on day 3, so a normal day-3 FSH does not confirm normal ovarian reserve. Other tests of ovarian reserve that are sometimes utilized include the *clomiphene citrate challenge test (CCCT)* and *ultrasound* assessment of follicle numbers, called the *antral follicle count*.

INFERTILITY EVALUATION AND ADVANCED MATERNAL AGE

Infertility usually is diagnosed if a woman has not become pregnant after 1 year of unprotected intercourse (i.e., no contraceptive measures used). However, if she is 35 or older, the evaluation should begin after 6 months of trying unsuccessfully to conceive. If a couple has an obvious medical problem affecting their ability to conceive, such as absence of periods

(amenorrhea), sexual dysfunction, a history of pelvic disease, or prior surgery, they should begin the infertility evaluation immediately. Fertility tests may include ovulation detection and evaluation of the *fallopian tubes*, *cervix*, and *uterus*. The male partner will have a *semen analysis*. Most testing can be completed within 6 months, and appropriate treatment can be started immediately after the evaluation is completed.

Women who have a medical disorder, such as high blood pressure or diabetes, should talk with their clinical care provider before attempting pregnancy. It is important that health problems are under control. The clinical care provider may suggest a change in medication or general health care before pregnancy as there are increased risks for older women. Conditions such as high blood pressure or diabetes develop more commonly in women who conceive after age 35. Special monitoring and testing may be recommended during pregnancy. Preconception counseling is often beneficial as well. Children born to women over age 35 have a higher risk of chromosomal problems. Women can choose to discuss these risks with their clinical care provider or a genetic counselor prior to attempting pregnancy. Prenatal testing may be performed after conception to check for certain birth defects. *Amniocentesis* and *chorionic villus sampling* are two methods of prenatal testing. Blood testing and ultrasound also may be used as screening tests for certain birth defects. Many parents want to know as much about the pregnancy as possible so they can make informed decisions.

TREATMENT OPTIONS AND ALTERNATIVES

Assisted Reproductive Technologies

If a cause for infertility is identified, the clinical care provider may suggest a specific treatment. However, sometimes no specific problem is found, and the infertility is labeled as “unexplained.” With unexplained infertility, or when traditional treatments have failed, advanced infertility therapies such as *superovulation with timed intrauterine insemination (SO/IUI)* or *in vitro fertilization (IVF)* may be suggested. In an SO/IUI cycle, fertility medications are administered to start the growth of multiple eggs in the ovaries. When these eggs are ready to ovulate, the partner’s washed sperm is placed directly into a woman’s uterus. This procedure is called *intrauterine insemination (IUI)* and causes minimal discomfort. IVF involves removing the eggs and fertilizing them with the male partner’s sperm in the lab oratory and then transferring the resulting embryos to the uterus. Either procedure, as well as any infertility treatment, may be used

with donor sperm rather than sperm from the woman's partner. With any treatment, a woman's age affects the chance for pregnancy. In women over 40, the success rate of SO/IUI is generally less than 5% per cycle. This compares to success rates around 10% for women ages 35 to 40. IVF is more effective but also has relatively low success rates in women 40 and older, generally less than 20% per cycle. For more information on assisted reproductive technologies, refer to the ASRM patient information booklet titled *Assisted Reproductive Technologies*.

Egg Donation

If you are older, especially if you're over 42, and have not succeeded with other therapies, or if you have *premature ovarian failure (POF)*, also known as *early menopause*, your treatment options are limited. *Egg donation*, which involves the use of eggs donated by another woman who is typically in her 20s or early 30s, is highly successful. The high success rate with egg donation confirms that egg quality associated with age is the primary barrier to pregnancy in older women. If you are over 40, your chance of successful pregnancy is much higher in IVF cycles using *donor eggs*, but many couples or single women in their early 40s will choose to accept the lower chance of becoming pregnant and use their own eggs. By age 43, the chance of becoming pregnant through IVF is less than 5%, and by age 45, use of donor eggs is the only reasonable alternative.

In an egg donation cycle, the woman receiving the donated eggs is referred to as the "recipient." The egg donor receives fertility medications to stimulate the production of multiple eggs in her ovaries. At the same time, the egg recipient is given hormone therapy to prepare her uterus to receive the fertilized eggs (*embryos*). After the eggs are obtained from the donor, they are fertilized in the laboratory with sperm from the recipient's partner. Several days after fertilization, the embryos are transferred to the recipient's uterus. Any embryos that are not transferred may be frozen (*cryopreserved*) for a future cycle.

Donor-egg IVF offers a woman an opportunity to experience pregnancy, birth, and motherhood. The child, however, will not be genetically related to her but will be genetically related to the father and the egg donor. Many programs recommend counseling so that all parties in a donor-egg agreement understand the ethical, legal, psychological, and social issues involved. Because success depends heavily upon the quality of eggs that are donated, women in their 20s with proven fertility are ideal donors.

FERTILITY PRESERVATION

Women who wish to delay childbearing until their late 30s or early 40s may consider methods of fertility preservation such as freezing of embryos after IVF or retrieving and freezing eggs for later use. The success of embryo freezing (cryopreservation) is well established, but it requires that the woman have a male partner or use *donor sperm*. Egg freezing for preservation of fertility is a new technology that shows promise for success. Age remains a problem faced by women interested in using elective egg freezing. As the age of women undergoing egg freezing increases, the outcomes of assisted reproductive technology cycles utilizing their frozen eggs become less favorable.

PREIMPLANTATION GENETIC SCREENING

New technologies that will allow testing of embryos for chromosomal abnormalities are currently being investigated. This technology applies to embryos created during a cycle of IVF. It may be particularly useful for older women. With preimplantation genetic diagnosis (PGD), a small number of cells are removed from each embryo and genetically evaluated. Embryos for transfer to the mother's uterus would be selected from the chromosomally normal embryos. The hope is that this procedure will result in improved successful pregnancy rates and avoidance of transmission of an embryo with a genetic disorder.

SUMMARY

Fertility naturally declines as women get older. However, the time decline begins and the rate at which it progresses, vary widely in women, but always begin well before menopause. Generally, fertility begins to drop in your late 20s or early 30s and falls more rapidly after the age of 35. Women who decide to delay pregnancy until after age 35 should obtain information on appropriate testing and treatment while remaining realistic about the chances for success with infertility therapy. By learning about all of the options and being aware of their own needs and goals, a woman and her partner will be prepared to make the best decisions.

GLOSSARY

Amenorrhea. The complete absence or suppression of menstrual periods.

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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 abnormalities that may affect fetal development.

Antral follicle count. The number of fluid-filled follicles observed using ultrasound.

Atresia (ovarian). The natural process by which eggs age and degenerate.

Cervix. The lower narrow end of the uterus that connects the uterine cavity to the vagina.

Chorionic villus sampling. A procedure in which a small sample of cells is taken from the placenta early in a pregnancy for chromosomal testing.

Chromosomes. Rod-shaped structures located in the nucleus of a cell which contain hereditary (genetic) material. Humans have 23 pairs of chromosomes (46 total). Two of the 46 are the sex chromosomes, which are the X and Y chromosomes. Normally, females have two X chromosomes and males have one X and one Y chromosome.

Clomiphene citrate challenge test (CCCT). A test of ovarian reserve in which serum FSH is checked on days 3 and 10 of the menstrual cycle and clomiphene citrate is taken on days 5 through 9.

Corpus luteum. Literally, a “yellow body.” A mass of yellow tissue formed in the ovary from a mature follicle that has collapsed after releasing its egg at ovulation. The corpus luteum secretes estrogen and large quantities of progesterone, a hormone that prepares the lining of the uterus (endometrium) to support a pregnancy.

Cryopreserved (frozen). Sperm or embryos may be frozen and stored for future use.

Donor egg. An egg from a fertile woman that is donated to an infertile woman to be used in an assisted reproductive technology procedure such as IVF. The woman receiving the egg will not be biologically related to the child but will be the birth mother on record.

Donor sperm. The sperm donated by a fertile man who is not the recipient’s partner.

Down syndrome. A genetic disorder caused by the presence of an extra chromosome 21 and characterized by mental retardation, abnormal facial features, and medical problems such as heart defects.

Early menopause. Also called premature ovarian failure. Cessation of menstrual periods due to failure of the ovaries before age 40.

Eggs. Also called oocytes or ova. The female sex cells produced by the ovaries that, when fertilized by a male's sperm, produce embryos, the early form of human life.

Egg donation. The process of fertilizing eggs from a donor and transferring the resulting embryos to the recipient's uterus. The recipient will not be biologically related to the child, although she will be the birth mother on record.

Embryo. Earliest stage of human development after sperm fertilizes an egg.

Estradiol. The predominant estrogen (hormone) produced by the follicular cells of the ovary.

Estrogen. The female sex hormones produced by the ovaries responsible for the development of female sex characteristics. Estrogen is largely responsible for stimulating the uterine lining to thicken during the first half of the menstrual cycle in preparation for ovulation and possible pregnancy. Estradiol and estrone are the main two estrogens.

Fertilization. The fusion of sperm and egg.

Follicle. A fluid-filled sac located just beneath the surface of the ovary, containing an egg (oocyte) and cells that produce hormones. The sac increases in size and volume during the first half of the menstrual cycle and at ovulation, the follicle matures and ruptures, releasing the egg. As the follicle matures, it can be visualized by ultrasound.

Follicle-stimulating hormone (FSH). In women, FSH is the pituitary hormone responsible for stimulating follicular cells in the ovary to grow, stimulating egg development and the production of the female hormone estrogen. In the male, FSH is the pituitary hormone that travels through the bloodstream to the testes and helps stimulate them to manufacture sperm. FSH also can be given as a medication. The US trade names are FertinexTM, FollistimTM, and Gonal-FTM.

Genetic. Referring to inherited conditions, usually due to the genes located on the chromosomes.

Gestational carrier. A woman who agrees to have a couple's fertilized egg (embryo) implanted in her uterus. The gestational carrier carries the pregnancy for the couple, who usually has to adopt the child. The carrier does not provide the egg and is therefore not biologically (genetically) related to the child.

Hormone. A substance secreted from organs of the body, such as the pituitary gland, adrenal gland, or ovaries, that is carried by a bodily fluid such as blood to other organs or tissues where it exerts a specific action.

Hypothalamus. A thumb-sized area in the brain that controls many functions of the body, regulates the pituitary gland, and releases gonadotropin-releasing hormone (GnRH).

In vitro fertilization (IVF). A method of assisted reproduction that involves combining an egg with sperm in a laboratory dish. If the egg fertilizes and begins cell division, the resulting embryo is transferred into the woman's uterus where it hopefully will implant in the uterine lining and further develop. IVF bypasses the fallopian tubes and is usually the treatment choice for women who have badly damaged or absent tubes.

Infertility. Infertility is the result of a disease (an interruption, cessation, or disorder of body functions, systems, or organs) of the male or female reproductive tract that prevents the conception of a child or the ability to carry a pregnancy to delivery. The duration of unprotected intercourse with failure to conceive should be about 12 months before an infertility evaluation is undertaken, unless medical history, age, or physical findings dictate earlier evaluation and treatment.

Insemination. Placement of sperm via a syringe into a female's uterus or cervix for the purpose of producing a pregnancy.

Libido. Sexual drive and desire.

LH surge. The secretion, or surge, of large amounts of luteinizing hormone (LH) by the pituitary gland. This surge is the stimulus for ovulation to occur.

Luteinizing hormone (LH). In women, the pituitary hormone that triggers ovulation and stimulates the corpus luteum of the ovary to secrete progesterone and androgens during the second half of the menstrual cycle.

Menopause. Natural cessation of ovarian function and menstruation. It can occur between the ages of 42 and 56 but usually occurs around the age of 51, when the ovaries stop producing eggs and estrogen levels decline.

Miscarriage. The naturally occurring expulsion of a nonviable fetus and placenta from the uterus; also known as spontaneous abortion or pregnancy loss.

Morphology. The form, structure, and shape of sperm. At least 30% of the sperm in a semen sample should have oval heads and slightly curving tails.

Motility. The percentage of all moving sperm in a semen sample. Normally 50% or more are moving rapidly.

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.

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. The release of a mature egg from its developing follicle in the outer layer of the ovary. This usually occurs approximately 14 days preceding the next menstrual period (the 14th day of a 28-day cycle).

Pituitary gland. A small hormone-producing gland just beneath the

hypothalamus in the brain that controls the ovaries, thyroid, and adrenal glands. Ovarian function is controlled through the secretion of FSH and LH. Disorders of this gland may lead to irregular or absent ovulation in the female and abnormal sperm production in the male.

Premature ovarian failure. Cessation of menstrual periods due to failure of the ovaries before age 40. Also known as early menopause.

Progesterone. A female hormone secreted by the corpus luteum after ovulation during the second half of the menstrual cycle (luteal phase). It prepares the lining of the uterus (endometrium) for implantation of a fertilized egg and allows for complete shedding of the endometrium at the time of menstruation. In the event of pregnancy, the progesterone level remains stable beginning a week or so after conception.

Semen analysis. The microscopic examination of semen (the male ejaculate) to determine its volume, the number of sperm (sperm count), their shapes (morphology), and their ability to move (motility) in addition to other parameters.

Sperm. The male reproductive cells produced by the testes 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.

Superovulation with timed intrauterine insemination (SO/IUI). A procedure to facilitate fertilization. The woman is given ovulation-inducing drugs which cause her ovaries to produce multiple eggs. When the eggs are ready to be released, the woman is inseminated with her partner's sperm or donated sperm.

Testes. The two male reproductive glands located in the scrotum which produce testosterone and sperm.

Testosterone. In men, the primary male hormone produced by the testes. It is responsible for the development of sperm, male physical characteristics, and sex drive. Testosterone is also produced in small quantities by the ovaries in women.

Ultrasound. A picture of internal organs produced by high-frequency sound waves viewed as an image on a video screen; used to monitor growth of ovarian follicles or a fetus and to retrieve eggs. Ultrasound can be performed either abdominally or vaginally.

Uterus (womb). The hollow, muscular organ in the pelvis where 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.

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