Infertility In Women

WHAT IS FEMALE INFERTILITY?

Infertility is the failure of a couple to become pregnant after one year of regular, unprotected intercourse. In both men and women the fertility process is complex.

About 10% of couples who wish to have a baby are still unable to after a year of unprotected sex. About half of these couples can achieve pregnancy within two years after appropriate treatment of the woman, the man, or both. Even under ideal circumstances, the probability that a woman will get pregnant during a single menstrual cycle is only about 30%. And, when conception does occur, only 50% to 60% of pregnancies advance beyond week twenty. (The inability of a woman to produce a live birth because of abnormalities that cause miscarriages is called infecundity and is not discussed in detail in this report.)

Males and females each account for 40% of infertility. In the remaining 20%, either both partners are responsible or the cause is unclear. Although this report specifically addresses infertility in women, it is equally important for the male partner to be tested at the same time. [For more information, see the Well−Connected Report #67, Infertility in Men.]

HOW DOES THE FEMALE REPRODUCTIVE SYSTEM WORK?

The Reproductive System

The Primary Organs and Structures in the Reproductive System. The primary structures in the reproductive system are as follows:

- The uterus is a pear−shaped organ located between the bladder and lower intestine. It consists of two parts, the body and the cervix.
- When a woman is not pregnant the body of the uterus is about the size of a fist, with its walls collapsed and flattened against each other. During pregnancy the walls of the uterus are pushed apart as the fetus grows.
- The cervix is the lower portion of the uterus. It has a canal opening into the vagina with an opening called the os, which allows menstrual blood to flow out of the uterus into the vagina.
- Leading off each side of the body of the uterus are two tubes known as the fallopian tubes. Near the end of each tube is an ovary.
- Ovaries are egg−producing organs that hold between 200,000 and 400,000 follicles (from folliculus, meaning "sack" in Latin). These cellular sacks contain the materials needed to produce ripened eggs, or ova.
- The inner lining of the uterus is called the endometrium, and during pregnancy it thickens and becomes enriched with blood vessels to house and support the growing fetus. If pregnancy does not occur, the endometrium is shed as part of the menstrual flow. Menstrual flow also consists of blood and mucus from the cervix and vagina.

Reproductive Hormones. The hypothalamus (an area in the brain) and the pituitary gland regulate the reproductive hormones. The pituitary gland is often referred to as the master gland because of its important role in many vital functions, many of which require hormones. In women, six key hormones serve as chemical messengers that regulate the reproductive system:

- The hypothalamus first releases the gonadotropin−releasing hormone (GnRH).
- This chemical, in turn, stimulates the pituitary gland to produce follicle−stimulating hormone (FSH) and luteinizing hormone (LH).
- Estrogen, progesterone, and the male hormone testosterone are secreted by the ovaries at the command of FSH and LH and complete the hormonal group necessary for reproductive health.

Ovulation. The process leading to fertility is very intricate. It depends on the healthy interaction of two sets of organs and hormone systems in both the male and female. In addition, reproduction is limited by the phases of female fertility. Nevertheless, this astonishing process results in conception within a year for about 80% of couples. Only 15% conceive within a month of their first attempts, however, and about 60% succeed after six months.

A woman's ability to produce children occurs after she enters puberty and begins to menstruate. The process to conception is complex:

- With the start of each menstrual cycle, follicle−stimulating hormone (FSH) stimulates several follicles to mature over a two−week period until their eggs nearly triple in size. Only one follicle becomes dominant, however, during a cycle.
- FSH signals this dominant follicle to produce estrogen, which enters the bloodstream and reaches the uterus. There, estrogen stimulates the cells in the uterine lining to reproduce, therefore thickening the walls.
- Estrogen levels reach their peak around the 14th day of the cycle (counting days beginning with the first day of a period). At that time, they trigger a surge of luteinizing hormone (LH).
LH serves two important roles:

- First, the LH surge around the 14th cycle day stimulates ovulation. It does this by causing the dominant follicle to burst and release its egg into one of the two fallopian tubes. Once in the fallopian tube, the egg is in place for fertilization.
- Next, LH causes the ruptured follicle to develop into the corpus luteum. The corpus luteum provides a source of estrogen and progesterone during pregnancy.

**Fertilization.** The so-called "fertile window" is six days long and starts five days before ovulation and ends the day of ovulation. Fertilization occurs as follows:

- The sperm can survive for up to three days once it enters the fallopian tube. The egg survives 12 to 24 hours unless it is fertilized by a sperm.
- If the egg is fertilized, about two to four days later it moves from the fallopian tube into the uterus where it is implanted in the uterine lining and begins its nine-month incubation.
- The placenta forms at the site of the implantation. The placenta is a thick blanket of blood vessels that nourishes the fertilized egg as it develops.
- The corpus luteum (the yellow tissue formed from the ruptured follicle) continues to produce estrogen and progesterone during pregnancy.

If the egg is not fertilized, the corpus luteum degenerates into a form called the corpus albicans, and estrogen and progesterone levels drop. Finally, the endometrial lining sloughs off and is shed during menstruation.

### Typical Menstrual Cycle

<table>
<thead>
<tr>
<th>Menstrual Phases</th>
<th>Typical No. of Days</th>
<th>Hormonal Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular (Proliferative) Phase</td>
<td>Cycle Days 1 through 6: Beginning of menstruation to end of blood flow.</td>
<td>Estrogen and progesterone start out at their lowest levels.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FSH levels rise to stimulate maturity of follicles. Ovaries start producing estrogen and levels rise, while progesterone remains low.</td>
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<tr>
<td></td>
<td>Cycle Days 7 – 13: The endometrium (the inner lining of the uterus) thickens to prepare for the egg implantation.</td>
<td></td>
</tr>
<tr>
<td>Ovulation</td>
<td>Cycle Day 14:</td>
<td>Surge in LH. Largest follicle bursts and releases egg into fallopian tube.</td>
</tr>
<tr>
<td>Luteal (Secretory) Phase, also known as the Premenstrual Phase</td>
<td>Cycle Days 15 – 28:</td>
<td>Ruptured follicle develops into corpus luteum, which produces progesterone. Progesterone and estrogen stimulate blanket of blood vessels to prepare for egg implantation.</td>
</tr>
<tr>
<td>If fertilization occurs:</td>
<td></td>
<td>Fertilized egg attaches to blanket of blood vessels that supplies nutrients for the developing placenta. Corpus luteum continues to produce estrogen and progesterone.</td>
</tr>
<tr>
<td>If fertilization does not occur:</td>
<td></td>
<td>Corpus luteum deteriorates. Estrogen and progesterone levels drop. The blood vessel lining sloughs off and menstruation begins.</td>
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### Stages and Features of Menstruation

**Onset of Menstruation (Menarche).** Previous evidence had set the onset of menstruation, called the menarche, at an average of age 12 or 13. Recent studies, however, set the time of onset earlier by about one year in Caucasian girls and two years in African American girls. Currently, the youngest possible age for normal puberty is 7 years old for Caucasians and 6 years old for African Americans, down from a previous low of 8 years for both.
Evidence is pointing to the increasing incidence of childhood obesity as a major cause of the trend in earlier menarche onset. (Obesity is also highly associated with hormonal disorders in girls entering puberty at young ages.) Environmental estrogens found in chemicals and pesticides are also suspects.

Length of Monthly Cycle. The menstrual cycle can be very irregular for the first one or two years, usually being longer than the average of 28 days. The length then generally stabilizes to an average of 28 days, although the cycle length may range from 20 to 45 days and still be considered normal. A variation of 10 days or more—either more or fewer days—may have an impact on fertility, however. When a woman reaches her 40s the cycle lengthens, reaching an average of 31 days by age 49. A number of factors can affect cycle length at any age.

<table>
<thead>
<tr>
<th>Risk Factors for Shorter Cycles</th>
<th>Risk Factors for Longer Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular alcohol use.</td>
<td>Being under 21 and over 44.</td>
</tr>
<tr>
<td>Stressful jobs.</td>
<td>Being very thin (also at risk for short bleeding periods).</td>
</tr>
<tr>
<td></td>
<td>Competitive athletics (also at risk for short bleeding periods).</td>
</tr>
</tbody>
</table>

Length of Periods. Periods average 6.6 days in young girls. By the age of 21, menstrual bleeding averages six days until women approach menopause. It should be noted, however, that about 5% of healthy women menstruate less than four days and 5% menstruate more than eight days.

Normal Absence of Menstruation. Normal absence of periods can occur in any woman under the following circumstances:

- Menstruation stops during the duration of pregnancy. Some women continue to have irregular bleeding during the first trimester. This bleeding may indicate a threatened miscarriage and requires immediate attention by the physician.
- When women breastfeed they are unlikely to ovulate. After that time, menstruation usually resumes and they are fertile again.
- Perimenopause starts when the intervals between periods begin to lengthen, and it ends with menopause itself (the complete cessation of menstruation). Menopause usually occurs at about age 51, although smokers often go through menopause earlier.

WHAT ARE THE RISK FACTORS FOR FEMALE INFERTILITY?

In the US, an estimated 10.2% of women between the ages of 15 to 44, or about 6.2 million women, have impaired fertility, and the incidence is increasing. About 25% of women experience some period of infertility during their reproductive years. Between 1982 and 1988 there was a 37% increase of infertile women between the ages of 35 to 44. The number of infertile women is expected to reach 6.3 million in the year 2000, and may be as high as 7.7 million in 2025.

Age

As a woman ages, her chances for fertility decline. Infertility in older women appears to be mostly due to a higher risk for chromosomal abnormalities that occur in her eggs as they age. Older women are also more likely to have health problems that may interfere with fertility. If fertilization occurs, older, healthy women can usually successfully bear a fetus to term, although they have a higher risk for miscarriage. Using population studies, experts have come up with estimated odds for pregnancy at different ages, given no fertility intervention. A 2002 analysis of pregnancy rates based on conception on the day of ovulation suggested that women between ages 19 to 26 have twice the pregnancy rates as those between 35 and 39.

<table>
<thead>
<tr>
<th>Chances for Pregnancy by Age</th>
<th>Fertility %</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Up until 34</td>
<td>90%</td>
</tr>
<tr>
<td>By age 40</td>
<td>Declining to 67%</td>
</tr>
<tr>
<td>By age 45</td>
<td>Declining to 15%</td>
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</table>

Weight Factors and Excessive Exercise

Although most of a woman's estrogen is manufactured in her ovaries, 30% is produced in fat cells by a process that transforms circulating adrenal male hormones into estrogen. Because a normal hormonal balance is essential for the process of conception, it is not surprising that extreme weight levels, either high or low, can contribute to infertility.

Being Overweight. Being overweight or obese (fat levels that are 10% to 15% above normal) can contribute to infertility in various ways. Obesity is highly associated with polycystic ovarian syndrome (PCOS), which is cause of
infertility in some cases. In one 2003 study, overweight women without PCOS were classified in one of five grades, depending on the severity of the obesity. The risk for irregular or absent periods increased two-fold by each increase in grade. In this group, amenorrhea (absent periods) was also highly associated with type 2 diabetes and blood sugar abnormalities.

**Being Underweight.** Body fat levels 10% to 15% below normal can completely shut down the reproductive process. Women at risk include the following:

- Women with eating disorders, such as anorexia or bulimia.
- Women on very low-calorie or restrictive diets are at risk, especially if their periods are irregular.
- Strict vegetarians might have difficulties if they lack important nutrients, such as vitamin B12, zinc, iron, and folic acid.
- Marathon runners, dancers, and others who exercise very intensely. (Lower body fat contributes to menstrual irregularities in competitive athletes, but other mechanisms are also involved.)

**Lifestyle Factors**

**Smoking.** Women who smoke one or more packs a day and those who started smoking before the age of 18 are at greater risk for infertility. Smoking also increases the risk for still births and low birth-weight babies. Male smokers also endanger fertility. Men who smoke have poorer sperm quality than nonsmokers, and they also have lower sex drives and have sex less frequently than nonsmokers. Heavy marijuana smoking appears to adversely affect fertility in both males and females.

**Caffeine.** A correlation has been found between caffeine consumption and infertility, possibly because has estrogen-like effects. Caffeine is found not only in coffee but also in tea, many soft drinks, chocolate, and a number of common medications.

**Alcohol.** Even moderate alcohol intake (as little as five drinks a week) can impair conception and also have adverse effects on the developing fetus.

**Vaginal Douching.** Vaginal douching can impair fertility and cause a number of gynecological problems. Studies suggest that it may contribute to infection, pelvic inflammatory disease, low-birth weight babies, preterm birth, and tubal pregnancy.

**Sexual Practices.** Sexual practices such as having multiple partners, not using condoms, and having intercourse during a period increase the risk for sexually transmitted organisms that can cause pelvic inflammatory disease leading to infertility.

**Environmental Risks**

**Hormone-Disrupting Chemicals.** Of particular concern is exposure to the following environmental hazards that might affect fertility. Estrogen-like chemicals or those that disrupt hormones are of particular concern for infertility in men and for effects on offspring women. Some being studied include the following:

- Diethylstilbestrol (DES), an estrogen compound, was used by some pregnant women in the 1940s and 1950s. The daughters of these women face a higher risk for cervical cancer, genital tract abnormalities, and miscarriage. However, DES does not appear to harm their granddaughter's reproductive capabilities.
- Bisphenol A is a widely used chemical found in plastic food containers and bottles that has provoked concern. It has potent estrogen-like effects in low dose. Use of the chemical in female rats has produced prostate abnormalities in their male offspring. However, it is not clear how such animal studies relate to people.
- Phthalates, chemicals used to soften plastics, are under particular scrutiny for their ability to disrupt hormones. Specific phthalates of special concern include dibutyl phthalate (DBP) and others found in many products, including cosmetics and clay products sold to children (Fimo, Sculpey). Animals exposed to phthalates have significantly impaired sperm count and abnormalities in reproductive structures, such as the testes. In addition, there is some concern that exposure in pregnant women may affect the offspring.
- Exposure to pesticides has caused known reproductive problems in animals and birds. Pesticides with estrogen-like effects include DDT, aldrin, dieldrin, PCPs, dioxins, and furans.
- There has been some concern that plant-based estrogens (phytoestrogens), such as the isoflavones found in soy and other foods, may reduce fertility rates. Sheep and quail grazing on plants containing phytoestrogens have had lower fertility rates. Studies to date on women who eat soy products have largely reported only positive health benefits and no effects on fertility but more research is required.
- Most evidence on the hormone of chemical estrogens has been reported in animals and birds. Tests of single chemicals containing estrogen have reported little danger for people. Some studies, suggest, however, that exposure to more than one of these chemicals may be very harmful. At this time, there is no strong evidence supporting a serious harmful effect in people who have normal exposure to these chemicals. Major efforts are underway to determine the extent of any possible harm from them.


**Exposure to Electromagnetic Waves or Microwave Emissions.** Heavy exposure to electromagnetic wave or microwave emissions has been linked to some reduced fertility in men. Although it is difficult to prove any risk on a developing fetus, research is very reassuring about ordinary exposure to low level emissions, such as those produced by small appliances.

**Stress and Fertility**

Similar neurotransmitters (chemical messengers) act in the hypothalamus gland, which controls both reproductive and stress hormones. Severely elevated levels of stress hormone can, in fact, shut down menstruation. Whether stress has any significant effect on fertility is unclear. There is some modest evidence that stress can affect the outcome of fertility treatments. One interesting small study reported a significantly higher incidence of pregnancy loss in women who experienced both high stress and prolonged menstrual cycles. Studies on any association between infertility and job stress have been inconclusive.

**WHAT CAUSES FEMALE INFERTILITY?**

Causes of infertility can be found in about 90% of infertility cases, but despite extensive tests, about 10% of couples will never know why they cannot conceive. Between 10% and 30% of cases of infertility have more than one cause. Male or female infertility each account for about 30% to 40% of cases. In men, sperm defects (their quality and quantity) are usually responsible. Female infertility is more complex.

**Pelvic Inflammatory Disease**

Pelvic inflammatory disease (PID) is the major cause of infertility worldwide. PID comprises a variety of infections caused by different bacteria that affect the reproductive organs, appendix, and parts of the intestine that lie in the pelvic area. The sites of infection most often implicated in infertility are in the fallopian tubes, a specific condition referred to as *salpingitis*.

**Causes of PID.** PID may result from many different conditions that cause infections. Among them are the following:

- Sexually transmitted diseases (cause of most PIDs). Chlamydia trachomatis is an infectious organism that causes 75% of infertility in the fallopian tubes. Gonorrhea is responsible for most of the remaining cases. Of concern is a 2002 report that suggests these disease may be widely under−diagnosed and undertreated.
- Pelvic tuberculosis (a growing global problem as tuberculosis cases increase).
- Nonsterile abortions.
- Ruptured appendix.
- Herpesvirus (suggested for some cases, but not confirmed as a causal agent).

**Symptoms of PID.** The infection may be subclinical (occurring without any symptoms), or there may be fever, chills, or pelvic pain indicating inflammation of the entire pelvic area.

**Effects of PID.** Severe or frequent attacks of PID can eventually cause scarring, abscess formation, and tubal damage that result in infertility. About 20% of women who develop symptomatic PID become infertile. PID also significantly increases the risk of ectopic pregnancy (fertilization in the fallopian tubes). The severity of the infection, not the number of the infections, appears to pose the greater risk for infertility. (A small US study suggests, however, that even mild Chlamydia infection that occurs in the upper genital tract may cause a higher proportion of ectopic pregnancies than previously thought.)

**Endometriosis**

The medical literature indicates that endometriosis may account for as many as 30% of infertility cases. Some evidence suggests that between 30% and 50% of women with endometriosis are infertile. Often, however, it is difficult to determine if endometriosis is the primary cause of infertility, particularly in women who have mild endometriosis. In an attempt to determine the chances for infertility with endometriosis, researchers have come up with a staging system based on findings during diagnostic surgery. [See Box Staging Endometriosis.]

It should be noted that endometriosis rarely causes an absolute inability to conceive, but, nevertheless, it can contribute to it both directly and indirectly.

**Direct Effect of Endometrial Cysts.** Endometrial cysts may directly prevent infertility in a number of ways.

- If implants occur in the fallopian tubes, they may block the egg's passage.
- Implants that occur in the ovaries prevent the release of the egg.
- Severe endometriosis can eventually form rigid webs of scar tissue (adhesions) between the uterus, ovaries, and fallopian tubes, thereby preventing the transfer of the egg to the tube.
**Immune Factors and the Inflammatory Response.** Researchers are focusing on defects in the immune system that not only may be responsible for endometriosis in the first place but may also cause the infertility associated with endometriosis. Even in early stage endometriosis, investigators have observed increased immune system activity.

**Other Conditions Linking Endometriosis and Infertility.** Researchers have sometimes noted unusually low levels of specific substances that enable a fertilized egg to adhere to the uterine lining. (Such abnormalities are more often a factor in infertility in women with mild to moderate endometriosis than in those with severe cases.)

One study found that the eggs in women with endometriosis appeared to have more genetic abnormalities than those in women without the disorder.

[For more information, see Well−Connected Report #74, Endometriosis.]

**Polycystic Ovarian Syndrome**

Polycystic ovarian syndrome (PCOS) is a condition in which the ovaries produce high amounts of androgens (male hormones), particularly testosterone. PCOS occurs in about 6% of women, and amenorrhea or oligomenorrhea (infrequent menses) is quite common. According to a 2002 study, nearly 30% of obese women with PCOS had amenorrhea. (The rate was lower—4.7%—in obese women with normal weight.)

In PCOS, increased androgen production produces high LH levels and low FSH levels, so that follicles are prevented from producing a mature egg. Without egg production, the follicles swell with fluid and form into cysts. Every time an egg is trapped within the follicle, another cyst forms, so the ovary swells, sometimes reaching the size of a grapefruit.

Without ovulation, progesterone is no longer produced, whereas estrogen levels remain normal.

The elevated levels of androgens (hyperandrogenism) can cause obesity, facial hair, and acne, although not all women with PCOS have such symptoms. Other male characteristics, such as deepening voice and clitoral enlargement, are rare.

PCOS also poses a high risk for insulin resistance, particularly in women who are also obese. Insulin resistance is associated with diabetes type 2, in which insulin levels are normal or high but the body cannot use this hormone efficiently. About half of PCOS patients, in fact, also have diabetes.

The drug valproate used to treat seizures and bipolar disease has been associated with PCOS. In most cases, the cause of PCOS is unknown.

**Premature Ovarian Failure (Early Menopause)**

Premature ovarian failure (POF) is the early depletion of follicles before age 40, which, in most cases, leads to premature menopause. It affects about 1% of women and is typically preceded by irregular periods, which might continue for years. In this condition follicle−stimulating hormone (FSH) are elevated, as they are during perimenopause. Premature ovarian failure is a significant cause of infertility and women who have this condition have only a 5% to 10% chance to conceive without fertility treatments.

**Causes of Premature Ovarian Failure.** There are a number of causes of POF. Often the cause of this disorder or other causes of POF is unknown. In some cases may represent an acceleration of the aging process.

The following may conditions may produce POF:

- Adrenal, pituitary, or thyroid gland deficiencies.
- Genetic factors related to the X chromosome. A woman needs two functioning X chromosomes for normal reproduction. When one is abnormal, ovarian function fails. The most severe example is Turner's syndrome, a genetic condition, in which one of the two X−chromosomes is missing or malfunctioning. Milder cases of ovarian failure can occur in fragile X syndrome and other rare inherited conditions that cause partial X−chromosome abnormalities.
- Other genetic factors. Some cases of POF and amenorrhea may be due to other genetic abnormalities. For example, researchers have reported POF in women with genetic defects in the production of growth factors called inhibins, which are produced by the ovaries. As yet, however, investigators have not identified specific genetic factors that might explain many cases of POF.
- Cancer treatments (radiation, chemotherapy, or both). Women who are undergoing such treatments and who want to become pregnant should ask about assisted reproductive technologies, possibly freezing embryos before their cancer treatments, which gives them the best odds. Ovarian transplantation procedures are under investigation. Investigators are testing a hormone called a gonadotropin−releasing hormone analogue that puts women in a temporary pre−pubescent state during chemotherapy and which may preserve fertility in many women.
- Autoimmunity. Autoimmune diseases, including diabetes type 1, systemic lupus erythematosus, autoimmune hypothyroidism, and autoimmune Addison's disease, are associated with a higher risk for early menopause. Autoimmunity, however, may also play a role in some cases of POF without the presence of specific
autoimmune diseases. In such cases, antibodies specifically attack the cells that secrete reproductive hormones thus causing ovarian failure.

Other causes: sarcoidosis, mumps, some sexually transmitted diseases, and tuberculosis. Women with epilepsy are at higher risk for POF.

**Idiopathic Hypogonadotropic Hypogonadism**

Idiopathic hypogonadotropic hypogonadism is a rare condition in which follicle-stimulating hormone (FSH) and luteinizing hormone (LH) are underproduced and prevent the development of functional ovaries. There are no other abnormalities in the hypothalamus-pituitary axis (such as tumors or abnormal stress hormones or prolactin). In most cases, the causes of hypergonadotropic hypogonadism are unknown. Genetic factors, including Kallman’s syndrome, have been identified in about 20% of these cases.

**Functional Hypothalamic Amenorrhea (FHA) and Eating Disorders**

Functional hypothalamic amenorrhea (FHA) is the absence of menstruation due to disturbances in the thyroid gland and hypothalamus-pituitary-adrenal (HPA) system, which regulates reproduction and other important functions. The eating disorders anorexia and bulimia are most often associated with FHA. FHA may be due to other different factors, most unknown.

**Luteal Phase Defect (Implantation Failure)**

Luteal phase defect is a general term referring to problems in the corpus luteum that result in inadequate production of progesterone. Because progesterone is necessary for thickening and preparing the uterine lining, the ovum fails to successfully implant in the endometrium. Between 25% and 60% of women who experience recurrent miscarriages may have a luteal phase defect. A luteal phase defect, however, can also occur in fertile women, so other factors may be responsible for implantation failure.

**Benign Uterine Fibroids**

Benign fibroid tumors in the uterus are extremely common in women in their 30s. The effect of fibroids on fertility is controversial. A 2002 analysis suggested that they may account for infertility in only 1% to 2.4% of women who are having trouble conceiving.

Large fibroids may cause infertility impairing the uterine lining, by blocking the fallopian tube, or by distorting the shape of the uterine cavity or altering the position of the cervix.

Some evidence suggests that even small fibroids may reduce the chances of pregnancy in women who are undergoing assisted reproductive techniques. Treatments to reduce fibroids may be helpful in such women, although there has been little research on this subject. [For more information, see Well-Connected Report #73, Fibroids: Uterine.]

**Elevated Prolactin Levels (Hyperprolactinemia)**

Prolactin is a hormone produced in the pituitary gland that stimulates breast development and milk production in association with pregnancy. High levels of prolactin (hyperprolactinemia) reduce gonadotropin hormones and inhibit ovulation. Hyperprolactinemia in women who are not pregnant or nursing can be caused by hypothyroidism or pituitary adenomas. (These are benign tumors that secrete prolactin. They can cause headache and visual problems as well as breast secretions.) Some drugs, including oral contraceptives and some antipsychotic drugs, can also elevate levels of prolactin.

Secretions from the breast not related to pregnancy or nursing (called galactorrhea) is a telltale symptom of high prolactin levels and should be investigated.

**Structural Problems Causing Obstruction**

*Inborn Abnormalities.* Inborn genital tract abnormalities may cause infertility. Mullerian agenesis is a specific malformation in which no vagina or uterus develops. Even in these cases, some women can become mothers by undergoing in vitro fertilization and having the fertilized egg implanted in another woman who is willing and able to carry the pregnancy (a surrogate mother).

*Uterine or Abdominal Scarring.* Bands of scar tissue that bind together after abdominal or pelvic surgery or infection (called adhesions) can restrict the movement of ovaries and fallopian tubes and may cause infertility. Asherman’s syndrome, for example, is scarring in the uterus that can cause obstructions and secondary amenorrhea. It may be caused by surgery, repeated injury, or unknown factors. Laparoscopic surgery is less likely to cause adhesions than standard open surgery.
In some of these cases surgery, may be helpful. One technique called pressure lavage under ultrasound guidance (PLUG) may prove to be useful for treating some cases of mild scarring in the uterus (intrauterine adhesions). This technique is based on transvaginal sonohysterography, which uses ultrasound along with saline infused into the uterus to enhance visualization. Continuous accumulation of saline in the procedure is used to break up the scars.

Other Causes of Infertility

**Ectopic Pregnancies.** Ectopic pregnancies increase the risk for infertility, although subsequent pregnancy rates are quite variable. Ectopic pregnancies that terminate without treatment appear to pose a lower risk for future infertility. Even a ruptured tube does not appear to reduce the chance for a future pregnancy in most women. Such an event however can be dangerous and even life threatening for the woman. Laparoscopic surgery to remove a fallopian tube affected by an ectopic pregnancy may preserve fertility better than traditional abdominal surgery.

**Cancer Treatments.** Cancer treatments (radiation or chemotherapy) can result in infertility. Women who are undergoing such treatments and who want to become pregnant should ask about assisted reproductive technologies and freezing embryos before their cancer treatments. This gives them the best chances for future child bearing.

**Medications.** Among the medications that can cause temporary infertility are those used to treat chronic disorders, as well as antidepressants, hormones, pain killers, and antipsychotic drugs.

**Inflammatory Bowel Disease.** Inflammatory bowel disease (particularly Crohn's disease or surgery for ulcerative colitis) can affect fertility.

**Celiac Sprue.** Celiac sprue is a disease in which the patient cannot tolerate gluten, a common food chemical. The disorder is also highly associated with infertility in men and women, possibly through multiple effects on nutrition, immune factors, and hormones. The mechanisms are not altogether clear, but infertility is usually reversible with strict dietary control.

**Epilepsy.** In one study of women with epilepsy, fertility rates were 33% lower than among women in the general population, perhaps due to certain antiepileptic drugs that increase the risk for birth defects. The social effects of epilepsy may also lead to marriage at an older age, which can be associated with delayed attempts to get pregnant and thereby affect fertility.

**Thyroid Problems.** Thyroid problems, either too much thyroid hormone (hyperthyroidism) or too little (hypothyroidism) can interrupt cycles.

**Metabolic Syndrome (also Called Syndrome X).** Doctors diagnose this condition when at least three of the there abnormalities are present: abdominal obesity, low HDL (good) cholesterol levels, high triglyceride levels, high blood pressure, and insulin resistance. Metabolic syndrome is a pre−diabetic condition that is significantly associated with heart disease. A 2002 study also reported that, as with PCOS, women with metabolic syndrome have higher levels of male hormones and are therefore at risk for infertility. A 2002 study estimated that 24% of the population now has this condition.

**Other Medical Conditions.** Medical conditions associated with delayed puberty and amenorrhea (absence of periods) include Cushing's disease, sickle cell disease, HIV, kidney disease, and diabetes. Genetic mutations that affect luteinizing hormone may also be responsible for some cases of light or absent menstruation. Other rare genetic disorders, such as Kallman syndrome, cause abnormalities in the hypothalamus of the brain.

**WHAT WILL CONFIRM THE DIAGNOSIS OF FEMALE INFERTILITY?**

In any fertility work−up, both male and female partners are tested if pregnancy fails to occur after a year of regular unprotected sexual intercourse. Fertility testing should be done earlier if a woman is over 35 years old or if either has known risk factors for infertility. It should be strongly stressed that an analysis of the man's semen should be performed before the female partner undergoes any invasive testing. [For more information, seeWell−Connected Report #67, Infertility in Men.]

**Medical History and Physical Examination**

The first step in any infertility work up is a complete medical history and physical examination. Sexual technique and timing, menstrual history, lifestyle issues (such as smoking and drug, alcohol, and caffeine consumption), any medications being taken, and a profile of the patient's general medical and emotional health can help the physician decide on appropriate tests.
Easy Preliminary Steps

Before embarking on an expensive fertility work-up, the following steps are free or low-cost and can be helpful:

- Monitor basal body temperature (See What Are Lifestyle Measures for Female Infertility?) This is accurate in determining if ovulation is actually taking place.
- Take an over-the-counter urine test for detecting LH surges. This helps determine the day of ovulation.

Laboratory Tests

A number of laboratory tests may be used for detecting the cause of infertility and for monitoring treatments:

Hormonal Levels. Blood and urine tests are taken to evaluate hormone levels. Hormonal tests for ovarian reserve (the number of follicles and quality of the eggs) are especially important for older women.

Examples of possible results include the following:

- High FSH and LH levels and low estrogen levels suggest premature ovarian failure or hypogonadotropic hypogonadism.
- High LH and low FSH may suggest polycystic ovary syndrome or luteal phase defect.
- High FSH and high estrogen levels on the third day of the cycle predicts poor success rates in older women trying fertility treatments.
- LH surges indicate ovulation.
- Blood tests for prolactin levels and thyroid function are also measured. These are hormones that may indirectly affect fertility.

Clomiphene Challenge Test. Clomiphene citrate (Clomid, Serophene), a standard fertility agent, may be used to test for ovarian reserve. With this test, the physician measures FSH on day 3 of the cycle. The woman takes clomiphene orally on the fifth and ninth days of the cycle. The physician measures FSH on the tenth day. High levels of FSH either on day three or day 10 indicate a poor chance for a successful outcome.

Tissue Samples. To rule out luteal phase defect, premature ovarian failure, and absence of ovulation, the physician may take tissue samples of the uterus one or two days before a period to determine if the corpus luteum is adequately producing progesterone. Tissue samples taken from the cervix may be cultured to rule out infection.

Tests for Autoimmune Disease. Tests for autoimmune disease, such as hypothyroidism and diabetes, should be considered in women with recent ovarian failure that is not caused by genetic abnormalities.

Imaging and Other Procedures

If an initial fertility work-up does not reveal abnormalities, in about 40% of cases, more extensive tests will reveal abnormal tubal or uterine findings. The three major approaches for examining the uterus are ultrasound (particularly a variation called saline–infusion sonohysterography), hysterosalpingography, and hysteroscopy. Although combinations of these diagnostic approaches are often used to confirm diagnoses, a 2000 study indicated that with the introduction of saline–infusion sonohysterography, all are equally accurate and combinations do not increase accuracy. Furthermore, the ultrasound procedure is significantly less painful than the other two, suggesting that this should be the procedure of choice, if available.

Ultrasound and Sonohysterography. Ultrasound is the standard imaging technique for evaluating the uterus and ovaries, detecting fibroids, ovarian cysts and tumors, and also obstructions in the urinary tract. It uses sound waves to produce an image of the organs and entails no risk and very little discomfort.

Transvaginal sonohysterography uses ultrasound along with saline infused into the uterus, which enhances the visualization of the uterus. This technique is proving to be more accurate than standard ultrasound in identifying potential problems. It is currently the gold standard for diagnosing polycystic ovaries.

Magnetic Resonance Imaging. Magnetic resonance imaging (MRI) gives a better image of any fibroids that might be causing bleeding, but it is expensive and not usually necessary.

Hysteroscopy. Hysteroscopy is a procedure that may be used to detect the presence of endometriosis, fibroids, polyps, pelvic scar tissue, and blockage at the ends of the fallopian tubes. Some of these conditions can be corrected during the procedure by cutting away any scar tissue that may be binding organs together or by destroying endometrial implants. (It may miss cases of uterine cancer, however, and is not a substitute for more invasive procedures, such as D&C or endometrial biopsy, if cancer is suspected.)

It is done in the office setting and requires no incisions. The procedure uses a long flexible or rigid tube called a hysteroscope, which is inserted into the vagina and through the cervix to reach the uterus. A fiber optic light source and
a tiny camera in the tube allow the physician to view the cavity. The uterus is filled with saline or carbon dioxide to inflate the cavity and provide better viewing. This frequently causes cramping.

There are small risks of bleeding, infection, and reactions to anesthesia. Many patients experience temporary discomfort in the shoulders after the operation due to residual carbon dioxide that puts pressure on the diaphragm. The wound itself is minimally painful.

**Hysterosalpingography.** Hysterosalpingography is performed to discover possible blockage in the fallopian tubes and abnormalities in the uterus.

- The physician inserts a tube into the cervix through which a special dye is injected. (The patient may experience some cramping and discomfort.)
- The dye passes into the uterus and up through the fallopian tubes.
- An x-ray is taken of the dye–filled uterus and tubes.
- If the dye is seen emerging from the end of the tube, no blockage is present. (In some cases, hysterosalpingography may even restore fertility by clearing away tiny tubal blockages.)
- If results show blockage or abnormalities, the test may need to be repeated. In case of blockage, hysterosalpingography may reveal a number of conditions, including endometrial polyps, fibroid tumors, or structural abnormalities of the uterus and tubes.

The test has significant rates of false diagnoses, both positive and negative. There is a small risk of pelvic infection, and antibiotics may be prescribed prior to the procedure. A 2002 study suggested that flushing the tubes with an oil–based medium (e.g., lipiodol) during this procedure may improve fertility rates in women with infertility of unknown causes.

**Investigative Tests to Determine Remaining Eggs**

As women age, the number of follicles (and therefore their egg supply) declines. Researchers are developing tests that may prove helpful in determining how many are left. Such tests include the following:

- Calculating the volume of the ovaries. In general, the smaller the ovaries, the fewer the remaining eggs.
- Counting antral follicles. Antral follicles are those that develop but do not become dominant follicles. Instead, they form a fluid–filled space called an antrum. Women who have fewer than three to five antral follicles appear to have a poor chance of fertility.
- Measuring inhibin B. Inhibin B is a growth factor produced in the ovaries. Low levels suggest fewer eggs.

Eventually these markers may be useful for determining which women need more aggressive treatments.

**Genetic Testing**

Genetic testing may be warranted in cases of male infertility or when genetic factors may be causing pregnancy failure in the woman. If genetic abnormalities are suspected in either partner, counseling is recommended.

A technique called preimplantation genetic diagnosis (PGD) is now available in some centers that can examine all the chromosomes in a human embryo. It helps identify abnormalities that increase the risk for infertility, treatment failures, or genetic defects in the offspring.

**WHAT ARE THE GENERAL GUIDELINES FOR FERTILITY TREATMENTS?**

Some authorities recommend that if a couple fails to conceive after one to two years during which unprotected sex has been sufficiently frequent, then they should consult a fertility expert. Women who are 35 or older, however, may want to begin exploring their options if they do not become pregnant within six months to a year.

**Fertility Treatment Approaches**

There are a number of approaches available for treating infertility, depending on the cause of the fertility: [See Table Treatments by Causes of Infertility.]

- Lifestyle measures (healthy life style, planning sexual activity with ovulation cycle, managing stress and emotions).
- Treatments for endometriosis, fibroids, or menstrual disorders. [For other details see the Well–Connected Reports #100, Menstrual Disorders: Cramps (Dysmenorrhea), #101, Menstrual Disorders: Absence of Periods (Amenorrhea), #80, Menstrual Disorders: Heavy Periods (Menorrhagia), #73, Fibroids: Uterine, or #74, Endometriosis.]
- Use of anti–estrogen agents, such as clomiphene, to induce ovulation in women with ovarian dysfunction.
- Surgery (standard or laparoscopic) to unblock fallopian tubes.
- Use of hormone treatments (clomiphene or progestins) for luteal phase defect.
• Assisted procedures, which are generally known as artificial insemination or assisted reproductive technologies (ART, with or without superovulation agents). [See Boxes Typical Regimen for Hyperstimulation and In Vitro Fertilization and Gentler Alternatives to Superovulation.] Treating the male partner for infertility, including artificial or intrauterine insemination with donor or partner sperm. [For more information, seeWell−Connected Report #67, Infertility in Men.]

Choosing a Fertility Clinic

Choosing a good fertility clinic is important. Those offering assisted reproductive techniques are not always regulated by the government, and abuses have been reported, including lack of informed consent, unauthorized use of embryos, and failure to routinely screen donors for disease.

The clinic should always provide the following information:

• The live−birth rate (not just pregnancy success rate) for other couples with similar infertility problems. (Multiple births, such as twins or triplets, are counted as one live birth.)
• Such statistics should include high−risk women, such as those who are older or fail to produce eggs. (Some disreputable clinics give success percentages that exclude high−risk women from their total, thereby making the percentage of success much higher.)

Advanced fertility procedures and medications are extremely expensive and often not covered by insurance. Warning: Couples should be cautious about offers of rebates in the event of failure; the clinics offering them are often significantly more expensive than those that don't. [For more information, seeWell−Connected Report #67, Infertility in Men.]

### Treatments by Causes of Infertility

<table>
<thead>
<tr>
<th>Causes of Infertility</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometriosis</td>
<td>Conservative surgery (typically laparoscopy) is the appropriate approach for restoring fertility. GnRH agonists or progestins, used to treat endometriosis itself, have no effect on fertility. Possible exceptions are GnRH agonists used after surgery. In one study, this treatment helped improve conception rates in women who subsequently underwent assisted reproductive techniques. Assisted reproductive technologies (ART). (Fertility drugs alone have no effect.) ART may be helpful for women with late−stage endometriosis. A 2002 study suggested that, of the ART procedures, in vitro fertilization may be more effective than artificial insemination in this population, but questions remain. It is not clear, in any case, whether either laparoscopy for removing endometrial implants or ART has additional advantages in many of these women compared to simply trying to become pregnant through non−aggressive means. [For more information, seeWell−Connected Report #74 Endometriosis.]</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Dopamine agonists, including bromocriptine (Parlodel) or cabergoline (Dostinex). Surgery in some cases.</td>
</tr>
<tr>
<td>Luteal phase defect</td>
<td>Clomiphene or superovulation agents (FSH agents or hMG).</td>
</tr>
<tr>
<td>Hyperprolactinemia (elevated prolactin)</td>
<td>Bromocriptine, cabergoline to shrink tumors that result in over secretion of prolactin. Cabergoline is more effective but bromocriptine has been used longer. Once ovulation starts, women who want to become pregnant should stop cabergoline one month before attempting conception. Surgery may be needed for women who do not respond to medications or who have large tumors.</td>
</tr>
<tr>
<td>Hypogonadotropic Hypogonadism</td>
<td>Fertility drugs (hMG preferable to FSH alone) with or without assisted reproductive technologies.</td>
</tr>
<tr>
<td>Pelvic Inflammatory Disease</td>
<td>Screening high−risk women for the presence of Chlamydia trachomatis and treating the organism before it causes symptoms could reduce the risk of PID by almost 60%. If any sexually transmitted infection is detected, both partners should receive antibiotics, even if there are no symptoms. If PID symptoms develop, particularly lower abdominal pain, fertility can be preserved if women receive antibiotics within two days. A delay significantly</td>
</tr>
</tbody>
</table>
**Polycystic Ovarian Syndrome**

- **Lifestyle changes** (e.g., weight loss and exercise in women who are overweight.)
  - Metformin (Glucophage), a diabetes agent used to restore insulin response. This agent and similar ones used in diabetes are showing great promise in reversing symptoms, reducing male hormones, and restoring regular menstrual cycles and ovulation in some women with PCOS. Studies suggest metformin might even improve fertility in nonobese women and in those who are not insulin resistant. Metformin also may improve outcome in women undergoing IVF.
  - Clomiphene or superovulation agents (FSH agents or hMG) with or without assisted reproductive technologies (ART).
  - Ovarian surgery. A procedure called ovarian drilling, in which the surgeon opens six to 12 small holes in the ovary, is showing promise and reduces the risk for multiple pregnancies compared to fertility treatments.

**Premature Ovarian Failure**

- **Assisted reproductive technologies with donor eggs.**

**Preserving fertility after cancer treatments**

- **Removal and freezing (called cryopreservation) of ovarian tissue containing embryos or freezing immature and unfertilized eggs to use for later reimplantation.** (Freezing before cancer treatment appears to offer the best chance.) Under investigation: Ovarian transplantation procedures and gonadotropin-releasing hormone analogues, which put women in a temporary pre-pubescent state during chemotherapy and may preserve fertility.

**Fallopian tubal blockage**

- **Surgical procedures (laparoscopy or salpingostomy) to clear the tubes.** (Average pregnancy rate after salpingostomy is about 30% but they can vary widely.)
  - Flushing the tubes with an oil-based medium (e.g., lipiodol) during hysterosalpingography (investigative). In a 2002 study, this procedure improved pregnancy rates in women with infertility of unknown causes.
  - Assisted reproductive technologies.

**Unexplained infertility**

- **Lifestyle measures, Fertility drugs, Assisted reproductive technologies.**

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### WHAT ARE LIFESTYLE MEASURES FOR FEMALE INFERTILITY?

#### Maintaining a Healthy Lifestyle

Although there are no dietary or nutritional cures for infertility, a healthy lifestyle is important. Ovulatory problems are reversible by changing behavioral patterns. Such conditions include:

- **Maintain a healthy weight.** Women who are either over- or underweight are at risk for fertility failure, including a lower chance for achieving success with fertility procedures. Everyone should have a diet rich in fresh fruits and vegetables, and whole grains and that is also low in saturated fats.
- **Stop smoking.** Smoking increases the risk for infertility in both men and women, and poses a future health risk for the mother and infant. Everyone should quit.
- **Avoid caffeine and alcohol.**
- **Avoid excessive exercise if it causes menstrual irregularity.** It should be strongly noted that moderate and regular exercise is essential for good health. Few women exercise to the extent that their periods are affected. For those that do, one study found that simply adding calories can restore menstruation in many cases. Competitive athletes, then, may not have to stop exercising to restore fertility, although more research is needed to confirm this.
- **Don't use electric blankets.** In one study, a 74% higher incidence of spontaneous abortion was associated with using an electric blanket during the month of conception. There was no association with heated waterbeds or electromagnetic waves.
- **Avoid any unnecessary medications.**

There is no evidence of harm to a developing fetus from low exposure to microwaves or electromagnetic waves. Women who remain anxious may derive comfort by avoiding some of these devices (such as cellular phones or electric blankets) and remaining a foot or so away from others (such as computers or microwave ovens).
Planning Sexual Activity and Monitoring Basal Body Temperature

Both male and female hormone levels fluctuate according to the time of day and they also vary from day to day and month to month. Some timing tips might be helpful.

**Male Hormone Levels and Sexual Activity.** Male hormone levels are highest in the morning. (Sexual interest also tends to be higher in the morning.) In one study of men, their sexual activity was highest in October, when conception rates were also high.

**Fertility and Seasonal Changes.** Different studies have reported higher sperm counts in the winter than in the summer. For women, fertility rates as measured by treatment success are highest in months when days are longest.

**Monitoring Basal Body Temperature.** To determine the most likely time of ovulation and therefore the time of fertility, a woman is instructed to take her body temperature, called her basal body temperature. This is the body's temperature as it rises and falls in accord with hormonal fluctuations.

- Each morning before rising, the woman takes her temperature with a specialized basal body thermometer and marks the result on a graph–paper chart. (Of interest is a wrist watch–like device under investigation that measures skin changes to predict ovulation.)
- The woman also notes the days of menstruation and sexual activity.
- The so-called “fertile window” is six days long and starts five days before ovulation and ends the day of ovulation.
- The chances for fertility are considered to be highest between days 10 and 17 in the menstrual cycle (with day 1 being the first day of the period and ovulation occurring about two weeks later). It should be noted, however, that a 2000 study reported that only 30% of women were fertile within the period of time. In the study, women had a 10% chance of ovulating on each day between day 6 and 21. Researchers who conducted the study suggested that each woman track the length of her cycle, which in the general population of women actually runs between 19 and 60 days. A long cycle, for example, suggests a delayed ovulation date.
- Immediately after ovulation the body temperature increases sharply in about 80% of cases. (Some women can be ovulating normally yet not show this temperature pattern.)

By studying the temperature patterns after a few months, couples can begin to anticipate ovulation and plan their sexual activity accordingly. Couples must try to avoid becoming fixated on the chart, however, in scheduling their sexual activity. Spontaneity can be lost, and the stress on the relationship can be quite severe, possibly impeding fertility.

**Hormone Monitoring Systems.** A device called a saliva fertility monitor (Fertility Tracker) uses a microscope to view slides containing saliva and monitors estrogen levels. Home test kits that monitor reproductive hormone levels in the urine (e.g., ClearBlue) are also available. They are less costly than the saliva test but are messier. Monitoring hormones levels helps to determine when a woman is ovulating.

**Frequency of Intercourse.** The question of how often a couple should have intercourse is in debate. Some experts say that having sex more than two days a week adds no benefits. And, in fact, frequent sexual activity lowers sperm count per ejaculation. Some studies have indicated, however, that having intercourse every day, or even several times a day, before and during ovulation improves pregnancy rates. Although sperm count per ejaculation is low, a constantly replenished semen supply is more likely to result in a fertilized egg.

Planning for Stress and Depression

The fertility process is a roller coaster of emotions that are present throughout and in both failure and success. There are almost no sure ways to predict which couples will eventually conceive. Some couples with multiple problems will overcome great odds, while other, seemingly fertile, couples fail to conceive. Many of the new treatments are remarkable, but a live birth is never guaranteed. The emotional burden on the couple is considerable and some planning is helpful.

**Planning for Emotional Turmoil.**

- Decide in advance how many and what kind of procedures will be emotionally and financially acceptable and attempt to determine a final limit. Fertility treatments are expensive. A successful pregnancy often depends on repeated attempts and the average cost is about $40,000. As of 2002, eight states required partial or full insurance coverage. (Some couples become addicted to treatment, and continue with fertility procedures until they are emotionally and financially drained.)
- Determine alternatives (adoption, donor sperm or egg, or having no children) as early as possible in the fertility process. This can reduce anxiety during treatments and feelings of hopelessness in case conception does not occur.

**Managing Emotional Stress During the Process.** Managing negative emotions can be viewed as important as medical treatment. A 2001 study, for example, reported that women undergoing fertility treatments who had the highest levels
of stress were 93% less likely to deliver a baby after five years compared to the most relaxed women. Women who were optimistic had a much higher likelihood of pregnancy. Other studies have also reported a significant association between psychologic factors, particularly anxiety, and fertility treatment failure. The following are some ways women reduce stress while trying to conceive:

- Talking to one's spouse, family, and friends is very beneficial. The best support comes from the spouse. Studies suggest that a positive attitude on the husband's part is essential for enabling his wife to deal effectively with either the success or failure of fertility treatments. It should be noted, however, that men and women may cope differently with the stress and each should understand the other's special needs. Women tend to want greater personal space and also to want to share the burden with their husbands. Men tend to cope by seeking to improve themselves (for example being strong, or being the "best").
- Almost half of women seeking fertility treatments practice good-luck rituals, including prayer and wearing charms or special jewelry. No evidence exists that these talismans increase fertility, but they may help reduce anxiety and enhance a sense of control.
- Cognitive-behavioral therapy, which uses methods that include relaxation training and stress-management, have been associated with higher pregnancy rates. (In one study, 42% became pregnant without medical intervention.)
- Acupuncture may help some women. Some evidence suggests that this alternative treatment has some beneficial effects on chemicals in the brain involved with stress and reproduction. In one intriguing study, women who were given acupuncture achieved significantly higher success rates during fertility treatments (42.5%) than those who were not given it (26.3%). Studies are needed to confirm any benefits.
- Attending support groups or counseling services for help before and after treatment helps many women endure the process and ease the grief should treatment fail. One study indicated that pregnancy rates were twice as high in women who coped with their depression by reaching out to others rather than repressing guilt or rage. (These results held only in cases in which women, not their mates, were infertile.)

Managing the Emotional Effects of the Outcome. After enduring the process, the couple must face the outcome, and even a positive outcome has emotional repercussions.

- Effects of Failure. Needless to say, the emotional stress of failure can be devastating even on the most loving and affectionate relationships and even in those who have prepared for the possibility of failure. Neither the male or female partner should hesitate to seek professional help if the emotional burdens are too heavy.
- Effects of Genetic Testing. As advanced technologies allow testing and greater genetic information at the earliest stage, potential parents will have to learn to deal with the uncertainties of possible chromosomal abnormalities, which may or may not be significant.
- Effects of Successful Treatments. Some studies have indicated that even if successful, some women experience higher stress and fear of failure during pregnancy. According to one 2000 study, however, women who achieved pregnancy using fertility treatments felt increasingly better and had higher self esteem and less anxiety as the pregnancy progressed than women whose pregnancies were not due to medical intervention.
- Effects of Multiple Births. A successful pregnancy that results in a multiple birth introduces new complexities and emotional problems. One study reported a very high rate of depression in women with triplets, particularly if they had little help from others, and especially if their husbands weren't involved.
- Effects on Parenting. Once the fertility treatment-assisted child arrives, parents (both men and women) are more likely to be anxious and to have less confidence than those who conceive naturally.

WHAT ARE FERTILITY DRUGS?

General Overview

Fertility drugs are often used alone as initial treatment to induce ovulation. If they fail as sole therapy, then they may be used with assisted reproductive procedures or artificial insemination to produce multiple eggs, a process called superovulation. [See Boxes Typical Regimen for Hyperstimulation and In Vitro Fertilization and Gentler Alternatives to Superovulation.]

Clomiphene

Clomiphene citrate (Clomid, Serophene) is usually the first fertility drug of choice for women with infrequent periods and long cycles. Unlike more potent agents used in superovulation, clomiphene is gentler and works by blocking estrogen, which tricks the pituitary into producing FSH and LH. This boosts follicle growth and the release of the egg. Clomiphene can be taken orally, is relatively inexpensive, and the risk for multiple births (about 5%, mostly twins) is lower than with other drugs.

Women with the best chances for success with this drug are those with the following conditions:

- Polycystic ovaries.
- Ability to menstruate but irregular menstrual cycle.
Women with poorer chances to no chances with this drug have the following conditions:

- Infertility but with normal ovulation.
- Women with low estrogen levels.
- Premature ovarian failure (i.e., early menopause).

One or two tablets are taken each day for five days, usually starting two to five days after the period starts. If successful, ovulation occurs about a week after the last pill has been taken. If ovulation does not occur, then a higher dose may be given for the next cycle. If this isn't successful, treatment may be prolonged or additional agents may be added. Experts usually do not recommend more than six cycles.

The drug often reduces the amount and quality of cervical mucous and may cause thinning of the uterine lining. In such cases, other hormonal agents may be given to restore thickness. Other side effects include ovarian cysts, hot flashes, nausea, headaches, weight gain, and fatigue. There is a 5% chance of having twins with this agent, and a slightly increased risk for miscarriage.

**Superovulation with Gonadotropins and GnRH Agonists**

Superovulation, also called controlled ovarian stimulation, is generally used if clomiphene does not work. This approach is the direct administration of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), collectively called gonadotropins. The intent is to mimic the natural process leading to ovulation and produce multiple follicles. Superovulation is generally used in conjunction with assisted reproductive technologies.

Many of the drugs used in superovulation are either taken from natural sources (menotropins) or are genetically developed:

- The standard agents are menotropins, which are hormones extracted from urine of postmenopausal or pregnant women. Menotropins contain high concentrations of FSH or LH. The specific agents that are administered either in combination or as FSH.
- Genetically developed hormones (called recombinant drugs) are proving to be very effective. These are pure hormonal agents and they are allowing the physician to better tailor the regimen to the unique needs of the patient.

**Human Menopausal Gonadotropins (hMG).** HMG (Pergonal, Repronal, Metrodin) is a menotropin that contains both FSH and LH and is obtained from the urine of postmenopausal women. HMG must be self-administered as an injection. It is one of the potent ovulation drugs now in use and is often used in assisted reproductive techniques. It may be effective in stimulating fertility in women with ovarian dysfunction, endometriosis, and unexplained infertility. HMG is administered as a series of injections two or three days after the period starts. Injections are usually given for seven to 12 days, but the time may be extended if ovulation does not occur. In such cases, an injection of human chorionic gonadotropin (hCG) may trigger ovulation [see below].

**FSH.** FSH stimulates the follicles directly and may be used with hCG to produce the LH and FSH surges that trigger ovulation. FSH is typically used alone for women who have taken clomiphene and failed. Such women often have polycystic ovaries, which is characterized by high LH and low FSH levels.

Urofollitropin (Metrodin, Fertinex, Bravelle) is a menotropin extracted from the urine of postmenopausal women and has been the standard FSH agent. Recombinant follicle-stimulating hormone (Puregon, Gonad−F, Follistim) is genetically developed form of the natural FSH. Therefore it has no risk for contaminants, such as urinary proteins or traces of LH, which can occur with menotropins. (Bravelle is a highly-purified menotropin and may be as effective as recombinant FSH.)

**Human Chorionic Gonadotropin (hCG).** Human chorionic gonadotropin or hCG is similar to luteinizing hormone and mimics the LH surge, which is to stimulate the follicle to release the egg. Standard hCG agents (APL, Follicutein, Pregnyl, Profasi, Humegen) are derived from the urine of pregnant women. The recombinant (genetically developed) form of hCG (Ovirdel) has fewer side effects at the injection site and its quality can be better controlled than the natural agents. It is generally used after hMG or FSH to stimulate the final maturation stages of the follicles. Ovulation, if it occurs, does so about 36 to 72 hours after administration.

**GnRH Analogs (Agonists or Antagonists).** Gonadotropin-releasing hormone analogs (GnRH−a) can be either GnRH agonists or antagonists. They are synthetic agents that are similar to natural GnRH but have very different actions. While natural GnRH stimulate a surge in LH, these agents actually prevent the LH surge that occurs right before ovulation. This action helps prevent the premature release of the eggs before they can be harvested for assisted reproductive technologies.

- GnRH agonists include leuprolide (Lupron), nafarelin (Synarel), goserelin (Zoladex), and buserelin.
- GnRH antagonists include ganirelix (Antagon) and cetorelix (Cetrotide). These are newer agents that are proving to simplify the procedure because of their quicker action compared to GnRH agonist. They appear to pose less of a risk for complications and side effects in the treatment process. It is not clear, however, if they
offer any advantages in achieving pregnancies.

GnRH–a agents are administered by injection or nasal spray. They increase the risk for ovarian cysts, but according to a 2000 study, they have no negative effect on pregnancy. These agents cause menopause–like effects, including hot flashes, vaginal dryness, insomnia, and possible osteoporosis (bone loss). Depression may be significant.

Complications of Superovulation

Multiple Births. Overproduction of follicles can lead to ovarian enlargement. This event increases the risk for multiple births. There is a 25% chance of multiple births (about 17% for twins and 8% for triplets and over).

Ovarian Hyperstimulation Syndrome. The most serious complication with superovulation is ovarian hyperstimulation syndrome (OHS), which is associated with the enlarged ovary (although the precise cause is unknown). This can result in dangerous fluid and electrolyte imbalances and endanger the liver and kidney. OHS is also associated with a higher risk for blood clots. In rare cases, it can be fatal. Symptoms include abdominal bloating, nausea, vomiting, and shortness of breath.

Bleeding and Rupture of Ovarian Cysts. Overproduction of follicles, if unchecked, may result in bleeding and rupture of ovarian cysts.

Cancer Concerns. There has been concern about an increased risk for ovarian and breast cancers in women taking fertility drugs, particularly clomiphene and human menopausal gonadotropins. In general, a strong body of evidence is finding no higher risk for either breast or ovarian cancer from the drugs themselves. Instead, such studies are suggesting that these cancers are caused by the same factors that contribute to the infertility itself. One exception, according to a 2003 study, may be a higher risk for breast cancer in women who took hMG for six or more months or cycles. The number of subjects was small, however, and more research is needed to confirm this finding.

Other Agents Used or Under Investigation

Tamoxifen. Tamoxifen (Nolvadex) is a drug known as a selective estrogen–receptor modulators (SERM). It is used to prevent breast cancer in high–risk women. Studies are also now suggesting that it may equal clomiphene in its ability to induce ovulation. It may be especially useful when used along with IVF for preserving fertility in breast cancer patients. This drug is less expensive than clomiphene and but poses some health hazards, including a risk for blood clots and uterine cancer.

Aromatase Inhibitors. Aromatase inhibitors block aromatase, an enzyme that is a major source of estrogen in many major body tissues. These agents include anastrozole (Arimidex) and letrozole, (Femara). Like tamoxifen, they are used for treating breast cancer and are being investigated for infertility in women. They do not appear to have the severe side effects of tamoxifen, however. In a 2002 comparison study between letrozole and clomiphene, the women who took letrozole had lower estrogen levels than those taking clomiphene. Evidence is suggesting that high estrogen levels may be harmful to the developing embryo. Therefore, letrozole may be more protective of the developing embryo than clomiphene.

Typical Regimen for Hyperstimulation and In Vitro Fertilization

Regimens to induce ovulation vary widely according to individual need. A typical procedure, involving superovulation and in vitro fertilization (IVF) may be as follows:

- Physicians make sure that the patient is not pregnant or in the luteal phase of her menstrual cycle (the premenstrual period).
- Injections of either hMG (which contains LH and FSH) or pure FSH are administered daily two to four days after day 1 of the next cycle. Either drug may be used.
- After four to eight days of treatment, estrogen levels are monitored. Increasing levels on the fourth day of treatment may be strong indicators of success. If estrogen levels indicate that ovaries are responding, ultrasound is then performed to detect possible overproduction of follicles. Such evaluation should then be conducted every one to two days and dosages adjusted accordingly.
- GnRH analogs are used to prevent a premature release of LH hormone (and therefore ovulation). GnRH agonists are typically administered either early on or a few days after ovulation in the cycle previous to the one planned for IVF. This approach is referred to as the long protocol and it serves to suppress the pituitary gland and allows time for the eggs to mature before harvesting. Other protocols using GnRH antagonists are under investigation, but to date the long protocol has the best pregnancy rates.
- When at least three follicles have reached a diameter of 18 mm, hCG is typically administered to release the egg. It is not given if there are signs of overproduction of follicles, which suggests a risk for ovarian hyperstimulation syndrome (OHS), a dangerous complication. (One study reported that administering high doses of progesterone in high–risk women the day of hCG administration may prevent OHS.)
- Egg retrieval may be performed about 36 hours following hCG administration, with the transfer of the embryo (the fertilized egg) back into the woman two or three days after retrieval.
Embryos are transferred to the uterus through a small tube. This process does not require an anesthetic, although the procedure can cause cramping.

### Gentler Alternatives to Superovulation

**Natural (Unstimulated) In Vitro Fertilization Cycles.** An alternative to superovulation for some couples is natural IVF cycles. It allows multiple, consecutive cycles of treatment. Natural IVF is far less expensive than standard hyperstimulation methods and avoids their risks, including multiple births and ovarian hyperstimulation syndrome (OHS).

- The process involves ultrasound and hormonal monitoring starting five days before the estimated ovulation day.
- No superovulation agents are used, such as FSH and hMG. The physician, however, may administer an injection of hCG to stimulate the LH surge.
- The egg retrieval timing is based on detecting LH surge.
- A single egg is retrieved. The procedure that follows is similar to other IVF cycles.

The basic disadvantage to this approach is that the eggs may be released before there is a chance for them to be harvested. Women report far lower stress levels with this approach, however, even though it requires more treatment cycles. In one 2001 study, the live-birth rate was 32%. Not all women are appropriate candidates, however. Women should have regular menstrual cycles and infertility of unknown cause or associated with problems in the fallopian tubes. Pregnancy rates are still very low in older women.

**Clomiphene.** Another gentler alternative to superovulation is the use of clomiphene before IVF, which works slightly better than unstimulated IVF.

### WHAT ARE ASSISTED REPRODUCTIVE TECHNOLOGIES?

Assisted reproductive technologies (ART) are procedures that either place sperm inside the woman or use donated eggs or employ techniques that retrieve eggs from the ovary and reimplant them. Fertilization may occur either in the laboratory or in the uterus. The number of live birth deliveries from ART increased by 73% between 1996 and 2000. And currently, 1% of all American babies—more than 35,000—are born each year using assisted reproductive technologies. In general, ART now achieves live births in more than 25% of cycles using fresh, nondonor eggs or embryos—up from 12% in 1988. (Actual pregnancy rates were higher, but some failed to come to term.)

The standard ART procedures are generally called artificial insemination (AI) and in vitro fertilization (IVF). To date no studies have compared the two approaches.

#### Artificial Insemination

Artificial insemination (AI) is the least complex of the assisted reproductive technologies and is often tried first in uncomplicated cases of infertility. AI either involves placing the sperm directly in the cervix (called intracervical insemination) or into the uterus (called intrauterine insemination, or IUI). IUI is the standard AI procedure.

It is useful under the following circumstances:

- When the woman's cervical mucus is unreceptive.
- When donor sperm are required.
- If the man's sperm count is very low (although it is preferable if at least five million per milliliter are motile).
- When unexplained infertility exists in both partners.

Those in whom AI fails, couples with specific fertility defects, or when the woman is older may be candidates for more advanced reproductive technologies. (One 2002 study reported, however, that IUI may be effective even in women over 40.)

**Pregnancy Rates.** A review of 45 studies reported that in unexplained infertility cases, the per-cycle pregnancy rates were 4% for intrauterine insemination (IUI) alone and 8% to 17% per cycle for IUI combined with superovulation, a procedure that uses fertility drugs to bolster egg recovery.

Researchers in 2002 study suggested IUI as a reasonable first option for many women under age 43. It is less expensive and poses less risk for multiple births than the more advanced assisted reproductive technologies (ART), such as in vitro fertilization. Although IVF procedures are more effective per cycle, couples tend to be able to afford more IUI cycles, so the pregnancy rates over time are very similar.

**The Artificial Insemination Procedure.** The AI procedure is as follows:
A woman usually (but not always) takes fertility drugs in advance. The man must produce sperm at the time the woman is ovulating. The sperm are subjected to certain so-called "washing" procedures. They are then inserted into the uterine cavity through a long, thin catheter.

The administration of fertility drugs and sperm retrieval is timed so that the process can be administered at the time of ovulation. Of interest was a 2000 study in which women who lay quietly for 10 minutes after sperm were implanted had a significantly higher rate of pregnancy than those who got up immediately.

**Standard In Vitro Fertilization (IVF)**

About 71% of ART procedures now use in vitro fertilization (IVF) with the woman's own eggs. An *in vitro* procedure is one that is performed in the laboratory. Advances in these procedures have dramatically increased the rate of live births. The best candidates for IVF are women with damaged fallopian tubes, and some experts believe it is a better option than attempting surgical repair. IVF is also used when infertility is unexplained or when the male partner has the infertility problem. A typical IVF procedure is as follows:

- The physician first induces superovulation using fertility drugs so that several eggs can be harvested from the ovary before they have been released from the follicles. Higher doses of fertility drugs for subsequent cycles do not appear to add any advantage in women who have a poor response the first time.
- To harvest eggs, the physician generally inserts a probe into the vagina and is guided by ultrasound. A needle is then used to drain the liquid from the follicles, and several eggs are retrieved.
- The eggs and sperm are combined in a Petri dish. Between 48 to 72 hours later the eggs are usually fertilized.
- The resulting embryos (the first stage toward the development of the fetus) are reimplanted into the woman's uterus.
- It takes about two weeks to determine if the process is successful.

IVF success rates for the first three cycles of treatment are about equal. They then decline modestly for the fourth cycle and drop significantly after the fifth cycle. [See Success Rates, below.]

Gamete/Zygote Intrafallopian Transfer. Gamete intrafallopian transfer (GIFT) and zygote intrafallopian transfer (ZIFT) are adaptations of IVF. GIFT and ZIFT are used in unexplained female infertility and in mild male infertility. The success rates are similar to those of IVF, but a woman must have at least one functioning fallopian tube.

**GIFT:** The procedure is as follows:

- The eggs are harvested as in IVF.
- They are mixed with the sperm but not actively fertilized.
- They are immediately injected back into the woman. Laparoscopy, a technique that employs a miniature viewing device, is used with this procedure to guide the placement of the embryos or egg through a long, thin catheter into the fallopian tubes.
- The sperm and egg are placed exactly where they would be in natural fertilization.

**ZIFT:** The procedure is as follows:

- The eggs are harvested as in IVF.
- They are then mixed with the sperm and, in this case, are fertilized in the laboratory.
- They are then implanted in the fallopian tubes as in GIFT. (The advantage of this procedure over GIFT is that the physician and couple are assured that fertilization has taken place and the eggs can be examined for defects before implantation.)

**Success Rates for Standard IVF Procedures**

In 2000, 1% of all American babies—more than 35,000—were born using IVF. In general, assisted reproductive technologies achieves live births in more than 25% of cycles using fresh, nondonor eggs or embryos—up from 12% in 1988. (Actual pregnancy rates were higher, but some failed to come to term.) About 35% of the ART–assisted live births in 2000 were multiple ones, with 4.3% being triplets or more.

Success rates have increased in all age groups (although they are still considerably lower in older than in younger women.) Chances for ART success are also greater among women who do not have uterine abnormalities and have had previous successful pregnancies.

The 2000 live–birth success rates by age are given in the following table:
** ART Procedure** | **Success Rate (Percentage of Cycles Resulting in Live Births)**  
--- | ---  
In vitro fertilization with fresh nondonor eggs (Includes GIFT and ZIFT rates, which do not differ significantly from each other.) | 28.3% to 22% women 22 to 25 | 35.2% to 28.4% women 25 to 35 | 28.4% to 25.6% women ages 35 to 37 | 22.4% to 15.2% women ages 38 to 40 | 11.7% to 8.1% women ages 41 to 42 | 2.2% and less women 43 and older.  

Success rates are also higher or lower depending on whether the woman uses her own eggs or whether they are donated and also whether the eggs are fresh or frozen. The highest rates are with donated fresh eggs (an average of 43.4% per transfer) and the lowest rates are when the woman's uses her own frozen eggs (a range of 22.3% per transfer for women under 35 to 14.6% for women 41 to 42.) It should be noted, however, that using frozen eggs is less expensive than fresh eggs, so the couple may be able to afford more cycles with frozen eggs.

**Use of Donor Eggs.** Older women are more likely to use donor eggs. In a 2002 study, success rates were the same for women who used donors with an age range of 20 to 40. There were also no differences in delivery rates for recipients up to age 45. Women over 45, however, increasingly had problems with implantation, pregnancy, and delivery.

**Use of Frozen Eggs.** Frozen eggs tend to have lower success rates because of toxins released by cells damaged in the freezing and thawing tissues. An interesting study in 2002 suggested that the use of lasers to remove these dead cells may increase the chances of success in the thawed embryos.

**Other IVF Techniques**

**In Vitro Maturation.** A new technique called in vitro maturation allows fertilization without the use of fertility drugs. In this process, follicles are harvested a few days before ovulation. In such cases, up to 50 have already begun to mature. At this time, about 15 of these maturing follicles can be removed, out of which two or three can produce healthy embryos.

**Blastocyst Transfer.** Blastocyst transfer is very promising. Instead of implanting the standard two- or three-day-old embryos in the uterus, the procedure implants blastocysts, which are more complex, five-day-old embryos. Fewer blastocysts than embryos need to be implanted, reducing the risk for multiple births. (There is, however, a higher risk for identical twins compared to other procedures.) Offspring may be more likely to be males than females. Pregnancy rates are about 36% with a first attempt but then drop significantly. The procedure is more likely to be successful in younger than older women.

**In Vitro Fertilization with Intracytoplasmic Sperm Injection (ICSI).** Intracytoplasmic sperm injection (ICSI) is one of a highly sophisticated group of techniques referred to as micromanipulation. ICSI injects one single sperm into an egg using microscopic instruments. It is used for couples who have failed IVF or when the man has severe infertility problems. It is proving to be effective even in some severe female fertility cases, and pregnancy rates are now equivalent to other ART techniques. The procedure itself is deceptively simple.

- A tiny glass tube (called a holding pipet) stabilizes the egg.
- A second glass tube (called the injection pipet) is employed to penetrate the egg's membrane and deposit a single sperm into the egg.
- The egg is released into a drop of cultured medium.
- If fertilized, the egg is allowed to develop for one or two days and then is either frozen or implanted.

The greatest concern with this procedure, if it is successful, is the risk of passing on any male genetic defects that caused infertility in the first place to the offspring. Studies in 2002 and 2003 reported no higher risks in birth defects in children born using ICSI procedures. One study that followed children to age five and reported a higher rate of certain rare disorders, notably Beckwith-Wiedemann syndrome. In such cases, the babies tend to be large with enlarged organs and a higher risk for certain cancers. Research is ongoing and more should be known about the procedure becomes more widespread and children get older. [See also What Are the Complications of Assisted Reproductive Technologies?]

Immature sperm (spermatids) are now being used in ICSI as well, and the long-term genetic implications of this remain unknown.
Ooplasmic Transfer.
Ooplasmic transfer is an experimental procedure that uses the woman's own egg and a female donor's egg and the male sperm for fertilization. Genetic material from the donor's egg plus the sperm are added to the woman's own egg. This has been successful in a few cases, but studies are very early and long-term effects are unknown. Research on this and similar procedures are currently conducted outside the US, where regulations have hindered investigation.

WHAT ARE THE COMPLICATIONS OF ASSISTED REPRODUCTIVE TECHNOLOGIES?

Multiple Births
Since ART procedures have become more widespread since 1980, multiple births have significantly increased. About 35% of all ART births are multiple ones, with 4.3% being triplets or more.

Complications from Multiple Births. Both the child and the mother are endangered by multiple births. The effects of multiple births on children are considerable:

- Higher rates of cesarean sections.
- Low birth weight.
- Higher mortality rates (13 times that of single births).
- Higher risks for later lung and heart problems.
- Higher risk for mental retardation or learning disabilities.

Limiting Birth Numbers. Given these hazards, the parents must make some hard decisions if the treatment produces multiple embryos. The choices are limited:

- Carry all of them to term, which increases health risks for both the mother and the developing fetuses.
- Complete abortion.
- Embryo reduction, in which the physician removes one or more embryos (possibly endangering the remaining embryos).

At this time, the best approach is to limit the number of implanted embryos in the first place. Experts are attempting to develop methods to reduce the risk for multiple births:

- Most centers now implant two to three embryos at a time, and the remainder can be frozen for future use. (To date, frozen eggs do not appear to pose a risk for developmental problems in children conceived using them, but follow-up studies are needed.) This limits the chance for success, but implanting more than three embryos only increases success rates very slightly, whereas the risk for multiple births increases significantly.
- Reducing the dosage of fertility drugs also reduces the risk for multiple births, but not significantly and it too reduces the chance for successful outcome.
- Blastocyst transfer may help reduce the chances for multiple births. [See above.]

Risks to the Woman
Studies suggest that there is a significantly higher risk for Caesarean sections (41.9% to 71.4%) after ART. In one small 2001 study, nearly 85% of those who had cesareans had no medical problems that warranted them. (This was a small Israeli study, however, and may not have widespread implications.) Of concern was a 2002 study reported a higher risk for pre-eclampsia (dangerously high blood pressure) in women who conceived with ART. More research is needed on this finding. There may also be a higher risk for urinary tract infections before delivery. It should be noted that infertile women in general have a poorer than average chance for full-term pregnancies regardless of whether they conceive spontaneously or with fertility treatments. In women using donor sperm from sperm banks, rare cases of AIDS, hepatitis, and other sexually transmitted diseases from infected sperm have been reported. Semen should be acquired only from a sperm bank licensed by either the state health department or the American Association of Tissue Banks.

Risk for Birth and Genetic Defects in Children
Several major studies have now reported a higher risk for low birth weight and birth defects in children born from assisted reproductive technologies. Low birth weight, in any case, is a well-known complication of multiple births, which are common with ART. However, even for single newborns delivered at term, 6.5% were underweight, compared to 2.5% in the general population. Another study found that 9% of children conceived with ART had major birth defects, including cleft lip or palate or problems with the feeding tube or windpipe, compared to 4.2% of babies conceived naturally. Birth defect rates were higher for single or multiple births as well as for births that reached term.

Still, ART remains a good option for many infertile couples. The likelihood of having a healthy single child of normal birth weight using ART is about 94%, and of having a child free of major birth defects 91%. In these studies, birth defect rates were similarly increased whether a child was conceived using Standard IVF or ICSI techniques. (There has
been some concern that ICSI specifically increased the risk for genetic problems.) To date, frozen eggs do not appear to pose any higher risk for developmental problems in children conceived using them, but follow-up studies are needed. Couples undergoing ART may have other factors, such as older age or genetic predispositions, which make complications more likely. If such procedures are found to be responsible, however, it is important that couples who undergo ART are aware of these issues. Preimplantation genetic diagnosis (PGD) is now available in a few fertility centers. It can help identify genetic defects in the offspring and may help parents determine future problems. Such testing, however, also raises significant emotional issues that should be addressed beforehand.

WHERE ELSE CAN HELP BE FOUND FOR INFERTILITY IN WOMEN?

RESOLVE, Inc. (www.resolve.org). Call 617–623–0744. This is the best support association for infertility. It publishes the National Summary and Fertility Clinic Reports. It provides names of fertility specialists and local associations.


American College of Obstetricians and Gynecologists (www.acog.org).


The Centers for Disease Control has an excellent site on the latest ART success rates at www.cdc.gov/nccdphp/drh/art.htm.


Society for Reproductive Endocrinology and Infertility (www.socrei.org).

Advanced Fertility Center of Chicago has interesting information on blastocysts at www.advancedfertility.com.

Polycystic Ovarian Syndrome Association (www.pcosupport.org).


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