AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE

MEDICATIONS FOR INDUCING OVULATION

A Guide for Patients

PATIENT INFORMATION SERIES

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

INTRODUCTION

Approximately 25% of infertile women have problems with *ovulation*. These include the inability to produce fully matured eggs or failure to "ovulate" (release) an egg. The inability to produce and/or release eggs is called *anovulation*. Fertility specialists utilize a group of medications, often called "fertility drugs," to temporarily correct ovulatory problems and increase a woman's chance for pregnancy. Fertility drugs may be used to correct other fertility problems such as improving ovarian hormone production to favorably affect the lining of the *uterus* (*endometrium*) in addition to inducing ovulation. These medications also may be used to stimulate the development of multiple eggs in certain circumstances, such as in an *in vitro fertilization* (IVF) cycle.

This booklet explains the basics of normal ovulation and the diagnosis and treatment of ovulatory problems. The specific applications for several types of ovulation drugs are presented, along with the intended results and possible side effects of each drug.

Nornal Reproductive Anatomy

The ovaries are two small glands, each about 1½ inches long and three-fourths of an inch wide located in a woman's pelvic cavity (Figure 1). They are attached to each side of the uterus (womb) by ligaments, near the *fallopian tubes*. About once a month, an egg matures in a *follicle* (a fluid-filled ovarian cyst containing the egg) after which it is released by one of the ovaries. The *fimbriae* (finger-like projections) of the fallopian tubes sweep over the ovary and move the egg into the tube. If sperm are present in the woman's reproductive tract, the egg may be fertilized in the tube. The fertilized egg (now called an *embryo*) begins to divide. The embryo travels through the tube and into the uterus where it implants in the endometrium (uterine lining). The embryo's journey through the tube takes four to five days.

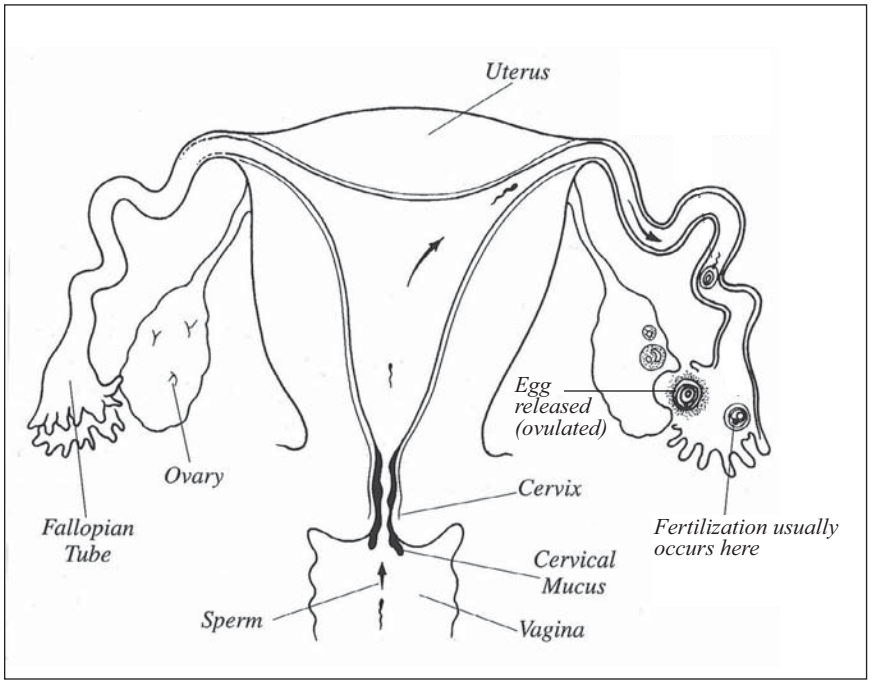

Figure 1. *Female reproductive tract*

The Menstrual Cycle

The menstrual cycle is divided into three phases: the *follicular phase*, the ovulatory phase, and the *luteal phase* (Figure 2).

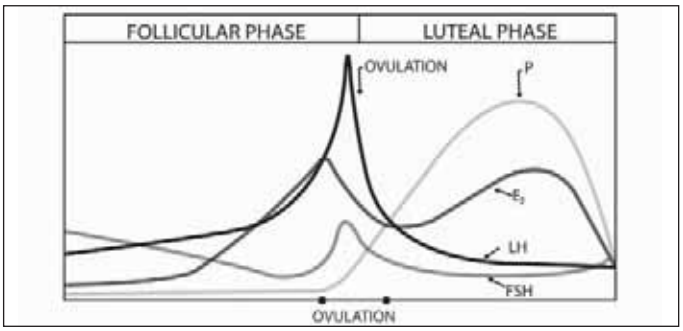

Figure 2. *Hormonal cycle in women with normal ovulation. The follicular phase is the phase in which the follicle is growing and secreting estrogen. The ovulatory phase is the 48-hour period characterized by the LH surge and the release of the egg (ovulation). The luteal phase is characterized by secretion of large amounts of progesterone and estrogen.*

The Follicular Phase

The follicular phase lasts about 10 to 14 days, beginning with the first day of menstruation and lasting until the *luteinizing hormone* (LH) surge. During the follicular phase, the *hypothalamus*, which is an area of the brain, releases *gonadotropin releasing hormone* (GnRH). This hormone tells the *pituitary gland*, located at the base of the brain, to release *follicle-stimulating hormone* (FSH). FSH stimulates, or triggers, the development of several follicles in the ovaries. These follicles contain immature eggs. One of these follicles will become the dominant follicle, and its egg will reach full maturity. The other follicles that were stimulated stop developing, and their eggs degenerate through a process called atresia. The dominant follicle increases in size and secretes, or sends out, *estrogen* into the bloodstream. The rising levels of estrogen cause the hypothalamus and pituitary to slow down the production of FSH, but prime the pituitary gland to respond to GnRH.

The Ovulatory Phase

The ovulatory phase begins with the *LH surge* and ends with ovulation, which is the release of the egg from the dominant follicle. As ovulation approaches, estrogen levels rise and trigger the pituitary gland to release a large surge of luteinizing hormone (LH). About 32 hours after the onset of this LH surge, the dominant follicle releases (ovulates) its egg.

The Luteal Phase

The luteal phase begins after ovulation and generally lasts about 12-16 days. After the egg is ovulated, the empty follicle that contained the egg becomes known as the *corpus luteum*. The corpus luteum secretes large amounts of *progesterone*, a hormone that helps prepare the endometrium for implantation of the embryo and pregnancy. If the egg is fertilized by a sperm, the resulting embryo reaches the uterus several days later and begins to implant in the endometrium. If an embryo does not implant, progesterone levels decline. The endometrium then breaks down, and is shed in the process of menstruation, and the cycle begins again.

Even though your cycles may continue to be regular in your 30s and 40s, the eggs that ovulate each month tend to be of poorer quality than those from your 20s. During this time in your life, your physician may wish to evaluate your *ovarian reserve*, which will help you understand your potential ability to get pregnant, based on the number and quality of eggs remaining in your ovaries.

DIAGNOSIS

Ovulation can be detected and confirmed in several ways. A woman who menstruates every 25 to 35 days probably is ovulating regularly. She also can assume that ovulation occurs about 14 days before the first day of each menstrual period. It is important to remember, however, that a woman can have randomly occurring uterine bleeding even though she never ovulates. Moreover, she also can have fairly regular cycles and not ovulate. There are several ways to detect ovulation, including commercially available ovulation prediction kits and basal body temperature (BBT) charts. Other diagnostic tests may be recommended before beginning treatment.

TREATMENT: OVULATION MEDICATION

Who Needs Ovulation Medication?

Medications for inducing ovulation are used to treat women who ovulate irregularly. Diagnosis of ovulatory dysfunction might be established by BBT recordings, monitoring urinary LH excretion, timed measurement of serum progesterone levels, timed endometrial biopsies and /or serial transvaginal *ultrasound* examinations. The causes of anovulation are varied. A diagnostic evaluation should be performed before medication is administered to stimulate ovulation. Whenever possible, treatment should be directed at correcting the underlying cause. Women might not ovulate because of *polycystic ovarian syndrome* (PCOS), insufficient production of LH and FSH by the pituitary, ovaries that do not respond well to normal levels of LH and FSH, thyroid disease, prolactin excess, obesity, eating disorders, or extreme weight loss or exercise. Sometimes the cause of anovulation cannot be identified confidently. Ovulation drugs are indicated in the treatment of women with amenorrhea (absence of menstruation) or irregular menstruation (*oligo-ovulatory*).

Ovulation drugs also can be used to stimulate the ovaries to produce more than one mature follicle per cycle, which leads to the release of multiple eggs. This *controlled ovarian hyperstimulatio*n (COH), or *superovulation*, may be accomplished with either oral or injectable fertility medications. Superovulation, combined with intrauterine *insemination* (IUI), is an empiric strategy for the treatment of several forms of infertility. The intent is to develop several mature eggs in hopes that at least one egg will be fertilized and result in pregnancy. Controlled ovarian hyperstimulation is also an important component of IVF treatment. For more information on IVF, consult the ASRM patient information booklet titled, *Assisted Reproductive Technologies*.

COMMONLY PRESCRIBED MEDICATIONS

The most commonly prescribed ovulation drugs are clomiphene citrate, FSH, *human chorionic gonadotropin* (hCG), and *human menopausal gonadotropin* (hMG). Bromocriptine, cabergoline, GnRH, GnRH analogs, insulin-sensitizing agents, and LH have very specialized applications that are described below. Table 1 on page 14 provides a summary of common ovulation drugs and their side effects.

Clomiphene Citrate

The most commonly prescribed ovulation drug is clomiphene citrate (CC). Brand names include Clomid® and Serophene®. This drug is most often used to stimulate ovulation in women who have infrequent or absent ovulation. It is also used in combination with IUI as an empiric treatment for unexplained infertility and mild endometriosis, particularly in young couples with a short duration of infertility, and in those who are unwilling or unable to pursue more aggressive therapies involving greater costs, risk, or logistical demands.

The standard dosage is 50 milligrams (mg) of CC per day for five consecutive days. Treatment begins early in the cycle, usually on the second, third, fourth or fifth day after menstruation begins. If a woman does not have periods, a period can be induced by administering progesterone or some other *progestin*. Ovulation rates, pregnancy rates, and pregnancy outcomes are similar regardless of whether treatment begins on cycle day 2, 3, 4 or 5. Clomiphene works by causing the pituitary gland to secrete more FSH. The higher level of FSH spurs the development of ovarian follicles that contain eggs. As the follicles grow, they secrete estrogen into the bloodstream. If treatment is successful, about a week after the last tablet of CC is taken, the pituitary is hypersensitive to GnRH and releases an LH surge. The LH surge causes the egg to be released from the mature follicle in a process called ovulation.

It is important to determine whether a given dosage of CC results in ovulation. Most doctors rely on the menstrual pattern, ovulation prediction kits, measurement of serum progesterone levels or the BBT chart to monitor a patient's response to the standard dose of clomiphene. A BBT chart is a chart in which the patient's body temperature upon awakening is plotted every morning

before she gets up. The readings help identify ovulation, which is indicated by a persistent temperature rise of one-half degree or more. If there is doubt, however, measuring the progesterone level about 14 to 18 days after the start of clomiphene, or examining the ovaries with ultrasound, can help to determine if and when ovulation occurred. If ovulation does not occur at the 50-mg dosage, CC may be increased by 50-mg increments in subsequent cycles until ovulation is achieved. Although dosages in excess of 100-mg are not approved by the Food and Drug Administration, your physician will determine the appropriate dose for you. Occasionally, the physician may choose to add other medications to clomiphene if the drug is not successful in inducing ovulation. For more information about BBT charts and ovulation detection, refer to the ASRM Patient Fact Sheet titled, *Ovulation Detection*.

Clomiphene can reduce the quantity and wateriness of cervical mucus, making it a barrier for sperm. Intrauterine insemination frequently is used in conjunction with CC. Clomiphene sometimes can alter endometrial thickness, making it thin and unreceptive to implantation.

The lowest dose of clomiphene sufficient to induce ovulation in anovulatory women is usually used for at least four to six cycles to provide an adequate trial for most patients. Clomiphene will induce ovulation in about 80% of properly selected patients. About 40% to 45% of couples receiving clomiphene citrate will become pregnant within six cycles. Most authorities suggest that clomiphene be given for no more than six cycles, because the chance of success is much less after six cycles. After that, alternatives may be considered. Women who have irregular or absent ovulation due to hypothalamic disorders, or who have very low estrogen levels, generally do not respond well to clomiphene. Women who are obese may have better success if weight is lost.

Clomiphene is generally tolerated well. Side effects are relatively common, but generally mild. Hot flashes occur in about 10% of women taking CC, and typically disappear soon after treatment ends. Mood swings, breast tenderness, and nausea are also common. Severe headaches or visual problems, such as blurred or double vision, are uncommon, and virtually always reversible. If these side effects occur, it is prudent to stop treatment immediately and call the physician. Women who conceive with clomiphene have approximately a 10% chance of having twins. Triplet and higher order pregnancies are rare (<1%), but may occur. There is no increased risk of miscarriage in pregnancies conceived with clomiphene therapy. Ovarian cysts, which can cause pelvic discomfort, may form as a result of the drug's overstimulation of the ovaries. A pelvic exam or ultrasound may be performed to look for ovarian cysts before beginning another clomiphene treatment cycle. A *luteal phase defect* may also occur. Side effects are more frequent with higher doses.

Aromatase Inhibitors

Aromatase inhibitors are medications that reduce estrogen levels. Although these medications are currently FDA approved for postmenopausal breast cancer, two drugs, letrozole (Femara®) and anastrozole (Arimidex®), have been used successfully for ovulation induction. Typically, the pills are prescribed for five days starting on cycle day 3, 4, or 5. Studies indicate that pregnancy rates are comparable to clomiphene citrate. The manufacturer of letrozole recently listed premenopausal endocrine status as a contraindication to its use. Recent data has raised concern that letrozole may be associated with an increased risk of congenital abnormalities.

Insulin Sensitizing Drugs

Insulin resistance and hyperinsulinemia are seen commonly in women with PCOS. Although most women with PCOS will ovulate with CC, many are resistant,and ultimately require an alternate treatment. A large majority of these women will have demonstrable insulin resistance.

When used alone for four to six months, insulin sensitizing agents such as metformin (Glucophage®) can restore cyclic ovulation and menses in many women with PCOS, although they are not currently approved by the FDA for this purpose. These medications are approved for the management of type 2 diabetes, where they work by improving the body's sensitivity to insulin. Many PCOS patients who fail to ovulate in response to either CC or metformin alone will respond when the two medications are used in combination. Gastrointestinal side effects of metformin are common and include nausea, vomiting and diarrhea. Since metformin therapy is associated with liver dysfunction, and rarely, a severe condition called lactic acidosis, liver and kidney function tests are performed periodically. Other diabetic drugs that improve insulin sensitivity, such as rosiglitazone (Avandia®) and pioglitazone (Actos®), also have been used for this purpose. For more information, please see the ASRM Fact Sheet titled, *Insulin Sensitizing Agents and PCOS.*

Gonadotropins

Gonadotropins are fertility medications that contain FSH or LH alone or in combination. A related medication is hCG, which is structurally similar to LH, and mimics the natural LH surge. There are a variety of commercially available gonadotropin preparations, and others are in various stages of research and development. Because of rapid changes in the international marketplace, the medications named in the sections below may not represent all of the formulations available in the United States and worldwide.

Gonadotropins often are prescribed for anovulatory women who have tried clomiphene without success. They are also used to help women whose pituitary glands do not produce adequate amounts of FSH and LH, and as a result these women have decreased estrogen and amenorrhea. Additionally, this drug is used to induce development of multiple follicles for fertility treatments, such as superovulation-IUI and IVF.

Human Menopausal Gonadotropin (hMG)

The first commercially available gonadotropin in the United States, hMG, contains approximately equal amounts of FSH and LH. The FSH and LH in hMG are extracted and purified from the urine of postmenopausal women who have high levels of these hormones. hMG is administered by injection, and directly stimulates the ovaries to induce the development and ovulation of one or more follicles.

Gonadotropin treatment involves a series of injections and careful monitoring during each treatment cycle. Use of gonadotropins may involve a certain amount of risk, expense, and inconvenience. With the use of hMG, women who are anovulatory, but have no other fertility problems may expect pregnancy rates approaching those of spontaneously ovulating women of the same age. Most physicians begin gonadotropin treatment on day 2 or 3 of the menstrual cycle. For non-IVF cycles, the usual starting dose is 75 to 150 units injected daily. Injections usually are administered over a period of 7 to 12 days, but may be extended if the ovaries are slow to respond. The follicle size is monitored with ultrasound, and the blood estrogen level may be measured frequently throughout treatment. If tests indicate that the ovaries are not responding to gonadotropins, the dose may be increased. The goal is to achieve one or more mature follicles, and an appropriate estrogen level, so that ovulation can be triggered by an hCG injection. If too many follicles develop, or if the estrogen level is too high, the physician may decide to withhold the hCG injection rather than risk *ovarian hyperstimulation syndrome* (OHSS) or a high-order multiple pregnancy.

Human Chorionic Gonadotropin

Produced in pregnant women by the placenta and extracted from the urine, hCG is similar in chemical structure and function to LH. As such, in a manner similar to the natural LH surge, an injection of hCG can cause the dominant follicle to release its egg. The physician may use ultrasound and blood estrogen levels to determine the day on which to administer hCG. Ovulation will usually occur 36 to 48 hours after hCG is administered. hCG is routinely used to trigger ovulation when gonadotropins are used to induce ovulation. hCG may also be used to trigger ovulation when CC is used to induce ovulation, particularly when a mid-cycle LH surge cannot be reliably detected. A pregnancy test (which measures hCG in the urine or blood) may be falsely positive if performed less than 10 days after hCG is administered.

Follicle Stimulating Hormone

In addition to the combination of FSH and LH found in menopausal gonadotropins, FSH, without significant LH, is available. There are two methods for obtaining this "pure" FSH, urinary extraction and through recombinant DNA technology. Early advances in extraction and separation techniques allowed for 99% of LH to be removed from hMG. The first urinary FSH product was introduced in 1986 (uFSH). Subsequently, more highly purified products were

developed. The application of tools used in molecular biology has allowed FSH to be produced by recombinant DNA technology (recFSH). In this technology, the portion of human DNA that controls FSH production is inserted into hamster cells that, when grown in culture, produce pure FSH indistinguishable from the human hormone. These products contain no LH. They are also administered via subcutaneous injection. As with hMG, these FSH medications bypass the hypothalamus and pituitary and directly stimulate follicular growth in the ovary. Pharmaceutical companies have introduced premixed ready-to-use gonadotropin formulations that reduce patient concerns about preparing their injections from separate vials of powder and liquid. Pen injector devices, analogous to those used for insulin-requiring diabetic patients, are safe, effective and easy for patients to use.

Luteinizing Hormone

An LH product produced by recombinant DNA technology recently has been introduced into the market (recLH). It is approved for use in combination with recFSH in anovulatory women with low levels of FSH and LH. Its role as a component of superovulation therapy is being studied.

Side effects of gonadotropins

There are potential risks and complications associated with the use of gonadotropins. Side effects should be discussed prior to taking these medications.

Despite intensive monitoring, up to 30% of gonadotropin-stimulated pregnancies are multiple. Of the multiple pregnancies, about two-thirds are twins and one-third are triplets or more. Premature delivery is a known risk for multiple pregnancies. The greater the number of fetuses in the uterus, the greater the risk of premature delivery. Premature delivery can subject the newborn to complications such as severe respiratory distress, intracranial hemorrhage, infection, cerebral palsy, and death. Some patients pregnant with triplets or more choose to undergo a procedure known as *multifetal pregnancy reduction* in an effort to decrease these risks.

The most serious side effect of gonadotropin therapy is ovarian hyper-stimulation syndrome (OHSS), in which the ovaries become swollen and painful. In severe cases, fluid accumulates in the abdominal cavity and chest. In about two percent of gonadotropin cycles, hyperstimulation may be severe enough to require hospitalization. Careful monitoring of ovulation induction cycles with the use of ultrasound and/or measurement of serum *estradiol* levels, in conjunction with daily adjustment of gonadotropin dosage, will enable the physician to identify risk factors and prevent most cases of severe OHSS. When serum estradiol levels are rapidly rising and/or too high, or an excessive number of ovarian follicles develop, one method of best prevention is to withhold further gonadotropin stimulation and delay hCG administration until estradiol levels plateau or decline. Alternately, hCG can be withheld so that ovulation fails to occur, thereby preventing severe OHSS.

Other potential side effects of gonadotropin treatment include breast tenderness, swelling or rash at the injection site, abdominal bloating, mood swings, and slight twinges of abdominal pain. Some women experience mood swings during gonadotropin therapy, although usually less severe than those that occur with clomiphene. It is difficult to separate the emotional changes due to the dramatic hormone shifts during gonadotropin therapy from the stress associated with this treatment. Regardless of the cause, a change in mood can be expected during gonadotropin therapy.

Bromocriptine and Cabergoline

Some women ovulate irregularly because their pituitary glands secrete too much *prolactin*. Increased blood levels of prolactin inhibit the release of FSH and LH, and therefore stop ovulation. The prolactin level is elevated in some women because the prolactin producing cells in the pituitary are hyperactive or form an *adenoma*. High prolactin levels (*hyperprolactinemia*) also can result from the use of certain drugs such as tranquilizers, hallucinogens, painkillers, alcohol, and, in rare cases, oral contraceptives. Disease of the kidney or thyroid may also raise prolactin levels.

Hyperprolactinemia often is treated with the medication bromocriptine or cabergoline, which reduces the amount of prolactin released by the pituitary. Parlodel® is the brand name for bromocriptine and Dostinex® is the brand name for cabergoline. These medications suppress prolactin production, and the blood prolactin level returns to normal in more than 90% of cases. Bromocriptine is taken orally as a tablet or capsule one to four times a day until the prolactin level is normal. It can also be administered vaginally. Cabergoline is taken as one to two tablets twice each week. Of the women treated, approximately 85% will ovulate and can become pregnant if no other causes of infertility are present. Bromocriptine and cabergoline treatment are usually discontinued during pregnancy. Women who fail to ovulate even after their prolactin levels are normal may be given clomiphene or gonadotropins along with bromocriptine and cabergoline.

Possible side effects of bromocriptine and cabergoline include nasal congestion, fatigue, drowsiness, headaches, nausea, vomiting, fainting, dizziness, and decreased blood pressure. For most patients, adjusting the dosage can eliminate these side effects. Some physicians start their patients on a very low dose and increase it gradually in an effort to prevent side effects. The risk of multiple pregnancies is not increased as a result of bromocriptine or cabergoline therapy.

Gonadotropin Releasing Hormone (GnRH)

GnRH is released from the hypothalamus in small amounts about once every 90 minutes. The pulsatile release of GnRH from the hypothalamus into the blood stream stimulates the pituitary gland to secrete LH and FSH. If GnRH is not being released properly, it can be administered in a pulsatile manner by a special drug delivery system that includes a belt holding a lightweight pump. The pump delivers a small volume of fluid every 60 to 90 minutes through a needle placed

beneath the skin (usually in the abdomen) or into a blood vessel. The risk and complications of GnRH, such as multiple births and ovarian hyperstimulation syndrome, are quite small.

GnRH Analogs (Agonists and Antagonists)

GnRH analogs are synthetic hormones similar to natural GnRH, but which are chemically modified. Leuprolide acetate, nafarelin acetate, and goserelin acetate are *GnRH agonists*. The normal pulsatile rhythmic release of GnRH from the hypothalamus stimulates the pituitary gland to secrete LH and FSH. However, when a woman takes a GnRH agonist, her pituitary gland is exposed to a constant, rather than a pulsatile, pattern of synthetic GnRH. After an initial acceleration in LH and FSH production, the pituitary then stops releasing these two hormones. This halts the production of ovarian hormones, ovulation is prevented, and estrogen levels are reduced.

Ganirelix acetate and cetrorelix acetate are *GnRH antagonists*, which suppress the production of FSH and LH without the initial stimulation. Both agonists and antagonists are ineffective when taken orally.

A GnRH analog often is used to prevent spontaneous ovulation when gonadotropins are given to women undergoing IVF. Both the GnRH agonist and antagonist can prevent the undesired secretion of LH, which can cause the follicles to release their eggs before they are harvested. Many infertility specialists believe that the addition of GnRH analogs during ovarian stimulation for IVF yields more mature eggs for fertilization and, therefore, more embryos for transfer.

The patient taking a GnRH antagonist or agonist long term often has temporary symptoms of menopause, including hot flashes, mood swings, and vaginal dryness. In addition, headaches, insomnia, decreased breast size, pain during intercourse, and bone loss may occur. These side effects are temporary, and the effect on the pituitary is completely reversible after GnRH agonists and GnRH antagonists are discontinued. In the course of ovulation induction, these side effects are rare.

LONG-TERM RISKS OF OVULATION DRUGS

After years of clinical use, physicians can advise patients confidently that clomiphene citrate and gonadotropins are not associated with an increased risk of birth defects. It has been suggested that women taking ovulation-inducing drugs such as clomiphene and gonadotropin may be at increased risk for ovarian cancer. Recent studies and re-analysis of earlier studies do not support this connection.

CONCLUSION

Lack of ovulation is very treatable. As a result of treatment, there is hope for many infertile couples of achieving their goal of having a child.

Table 1. *Ovulation Drugs, their brand names, and most common side effects*

Generic Name	Brand Name(s) (not all inclusive)	Form	Most Common Side Effects
Clomiphene citrate	Clomid® Serophene®	Tablets	• increased incidence of multiple births • thick, dry cervical mucus • hot flashes, nausea, breast tenderness • occasional headaches or blurred vision • depression, mood swings • ovarian cysts, pelvic discomfort
Metformin	Glucophage	Tablets	• gastrointestinal • lactic acidosis • liver dysfunction
Follicle Stimulating Hormone (FSH)	Urinary derived: Bravelle™ Recombinant DNA technology: Follistim™ (follitropin beta) Gonal-F® (follitropin alpha)	Injection	• increased incidence of multiple births • increased incidence of miscarriage and premature delivery • breast tenderness, swelling, or rash at injection site • mood swings, depression • mild to severe hyperstimulation syndrome (enlarged ovaries, abdominal pain, and bloating)
Luteinizing Hormone (LH)	Recombinant DNA technology: Luveris® (lutropin alpha)	Injection	• same as for FSH
Human Chorionic Gonadotropin (hCG)	Urinary derived: A.P.L.® Pregnyl® Novarel™ Recombinant DNA technology: Ovidrel® (choriogonadotropin alpha)	Injection	• no known side-effects if only taking hCG
Human Menopausal Gonadotropin (hMG)	Urinary derived: Repronex® Menopur®	Injection	• same as for FSH
Dopamine agonists	Parlodel® (bromocriptine) Dostinex® (cabergoline)	Tablets	• nausea, vomiting, nasal congestion • headache, dizziness, fainting • decreased blood pressure
Gonadotropin-Releasing Hormone (GnRH)	Factrel® Lutrepulse®	Injection	• slight chance of multiple births • mild hyper-stimulation syndrome • headache • nausea
GnRH Agonists*	Lupron Depot® (Leuprolide Acetate) Synarel® (Nafarelin Acetate) Zoladex® (Goserelin Acetate)	Injection Nasal spray Injectable implant	• hot flashes, headache • mood swings, insomnia • vaginal dryness • decreased breast size • painful intercourse • bone loss * symptoms occur in long-term use
GnRH Antagonists	Ganirelix Acetate Cetrotide® (cetrorelix acetate)	Injection	• same as GnRH Agonists

GLOSSARY

Adenoma. A type of benign (non-cancerous) pituitary tumor that may secrete excess amounts of prolactin or other hormones.
Amenorrhea. Absence of menstrual periods.
Anovulation. A condition in which a woman rarely or never ovulates.
Biopsy. A tissue sample taken for microscopic examination.
Bromocriptine. A drug used to suppress the pituitary gland's production of prolactin. Parlodel® is a brand name.
Cabergoline. A drug used to suppress the pituitary gland's production of prolactin. Dostinex™ is a brand name.
Cervix. The narrow, lower end of the uterus where it opens into the vagina.
Clomiphene citrate. An antiestrogen drug used to induce ovulation. Clomid® and Serophene® are brand names.
Controlled ovarian hyperstimulation (COH). Administration of fertility medications in order to achieve the development of two or more mature follicles. Also called superovulation.
Corpus luteum. A mature follicle that has collapsed after releasing its egg at ovulation. The corpus luteum secretes progesterone and estrogen during the second half of a normal menstrual cycle. The secreted progesterone prepares the lining of the uterus (endometrium) to support a pregnancy.
Embryo. The earliest stage of human development after a sperm fertilizes an egg.
Endometrium. Uterine lining that sheds monthly to produce a menstrual period.
Estradiol. The main estrogen (hormone) produced by the follicular cells of the ovary.
Estrogen. The female sex hormone produced by the ovaries that is responsible for the development of female sex characteristics. Estrogen is largely responsible for stimulating the uterine lining to thicken during the first half of the menstrual cycle in preparation for ovulation and possible pregnancy. It is also important for healthy bones and overall health. A small amount of this hormone is also made in the male testes.
Fallopian tubes. A pair of hollow tubes attached one on each side of the uterus. The egg travels from the ovary to the uterus through narrow passageways in the middle of these tubes.
Fimbriae. The finger-like projections of the fallopian tubes that sweep over the ovary and move the egg into the tube.
Follicle. A fluid-filled cyst located just beneath the surface of the ovary, containing an egg (oocyte) and cells that produce hormones. The sac increases in size and volume during the first half of the menstrual cycle and at ovulation, the follicle matures and ruptures, releasing the egg. As the follicle matures, it can be visualized by ultrasound.
Follicle Stimulating Hormone (FSH). In women, FSH is the pituitary hormone responsible for stimulating follicular cells in the ovary to grow, stimulating egg

development and the production of the female hormone estrogen. In the male, FSH is the pituitary hormone which travels through the bloodstream to the testes and helps stimulate them to manufacture sperm. FSH can also be given as a medication. The U.S. trade names are Fertinex™, Follistim™, and Gonal-F®.

Follicular phase. The first half of the menstrual cycle (beginning on day one of bleeding) during which the dominant follicle secretes large amounts of estrogen.

Gonadotropin Releasing Hormone (GnRH). The natural hormone secreted by the hypothalamus that prompts the pituitary gland to release follicle stimulating hormone (FSH) and luteinizing hormone (LH) into the bloodstream. This in turn stimulates the ovaries to produce estrogen, progesterone, and to ovulate. Factrel® and Lutrepulse® are brand names.

GnRH Agonists. Synthetic hormones similar to the naturally occurring gonadotropin-releasing hormone (GnRH) that initially stimulate and then subsequently decrease FSH and LH secretion from the pituitary gland.

GnRH Antagonists. Synthetic hormones that directly decrease FSH and LH secretion from the pituitary gland.

Human chorionic gonadotropin (hCG). A hormone produced by the placenta during pregnancy that is often used with clomiphene or hMG to cause ovulation.

Human menopausal gonadotropin (hMG). An ovulation drug containing a mixture of follicle stimulating hormone and luteinizing hormone derived from the urine of postmenopausal women.

Hyperprolactinemia. High levels of prolactin in the bloodstream.

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

In vitro fertilization (IVF). A method of assisted reproduction that involves surgically removing an egg from the woman's ovary and combining it with sperm in a laboratory dish. If the egg is fertilized, resulting in an embryo, the embryo is transferred to the woman's uterus.

Insemination. The deposit of semen through a syringe within the uterine cavity or cervix to facilitate fertilization of the egg.

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

Luteal phase. The second half of the menstrual cycle after ovulation when the corpus luteum secretes large amounts of progesterone.

Luteal phase defect. A shorter than normal luteal phase or one with lesser progesterone secretion despite a normal duration.

Luteinizing hormone (LH). The hormone that triggers ovulation and stimulates the corpus luteum to secrete progesterone.

Multifetal pregnancy reduction. Also known as selective reduction. A procedure to reduce the number of fetuses in the uterus. This procedure may be considered for women who are pregnant with multiple fetuses. As the risk of extreme premature delivery, miscarriage (spontaneous abortion), and other problems

increases with the number of fetuses present, this procedure may be performed in an attempt to prevent the entire pregnancy from aborting.
Oligo-ovulatory. A term describing a woman who ovulates infrequently.
Ovarian hyperstimulation syndrome (OHSS). A possible side-effect of treatment with human menopausal gonadotropin in which the ovaries become painful and swollen, and fluid may accumulate in the abdomen and chest.
Ovarian reserve. A woman's fertility potential in the absence of specific pathophysiologic changes in her reproductive system. Diminished ovarian reserve is associated with depletion in the number of eggs and worsening of oocyte quality.
Ovulation. The expulsion of a mature egg from its follicle in the outer layer of the ovary. It usually occurs on approximately day 14 of a 28 day cycle.
Pituitary gland. A small gland just beneath the hypothalamus that secretes follicle stimulating hormone and luteinizing hormone, which stimulate egg maturation and hormone production by the ovary.
Polycystic ovarian syndrome (PCOS). A condition characterized by chronic anovulation, excessive ovarian production of testosterone and/or ovaries with many small cystic follicles. Symptoms may include irregular or absent menstrual periods, obesity, infertility, excessive hair growth, and/or acne.
Progesterone. A female hormone secreted by the corpus luteum after ovulation during the second half of the menstrual cycle (luteal phase). It prepares the lining of the uterus (endometrium) for implantation of a fertilized egg and allows for complete shedding of the endometrium at the time of menstruation. In the event of pregnancy, the progesterone level remains stable beginning a week or so after conception.
Progestin. A synthetic hormone that acts similar to progesterone.
Prolactin. A pituitary hormone that stimulates milk production.
Superovulation. Administration of fertility medications in order to achieve the development of two or more mature follicles. Also called controlled ovarian hyperstimulation.
Ultrasound. High frequency sound waves that produce an image on a monitor screen of internal organs.
Uterus (Womb). The muscular organ in the pelvis where an embryo implants and grows during pregnancy. The lining of the uterus, called the endometrium, produces the monthly menstrual blood flow when there is no pregnancy.

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