AMERICAN SOCIETY FOR REPRODUCTIVE MEDICINE
Formerly The American Fertility Society

OVULATION DRUGS

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 one-third to one-half of all infertile women have problems with *ovulation*. This can include the ovaries' inability to produce mature eggs or "ovulate" (release) an egg. If no eggs are released, this is called *anovulation*. Infertility specialists rely on a certain group of ovulation drugs, often called "fertility drugs," to temporarily correct ovulatory problems and to increase a woman's pregnancy potential. Contrary to popular belief, these drugs do not make all women more fertile and in fact only work during the month in which the medications are taken. The drugs allow ovulation to occur more regularly in some women with ovulatory problems who may otherwise remain anovulatory and therefore infertile.

Ovulation drugs can control the time of ovulation and stimulate eggs to mature and be released. These drugs may be used to correct other infertility problems such as improving hormone production to favorably affect the lining of the *uterus* called the *endometrium*. These medications also can be used to stimulate the development of multiple eggs during the treatment cycle.

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

NORMAL OVULATION

The Process

The ovaries are two small glands, each about one-and-one-half to two inches long and three-fourths to one inch wide, located in a woman's pelvic

cavity (Figure 1). They are attached to the uterus (womb), one on each side, near the fimbriated (finger-like) openings of the *fallopian tubes*. About once a month, a mature egg is released by one of the ovaries. The fimbriae of the fallopian tubes sweep over the ovary and pick up the egg after it has been released from the follicle (the fluid-filled ovarian cyst containing the egg). If the egg is fertilized, which usually occurs in the tube, the resulting embryo (fertilized egg) continues to mature and increase its number of cells as it travels to the uterus and implants in the endometrium (uterine lining). The embryo's full journey through the tube takes four to five days.

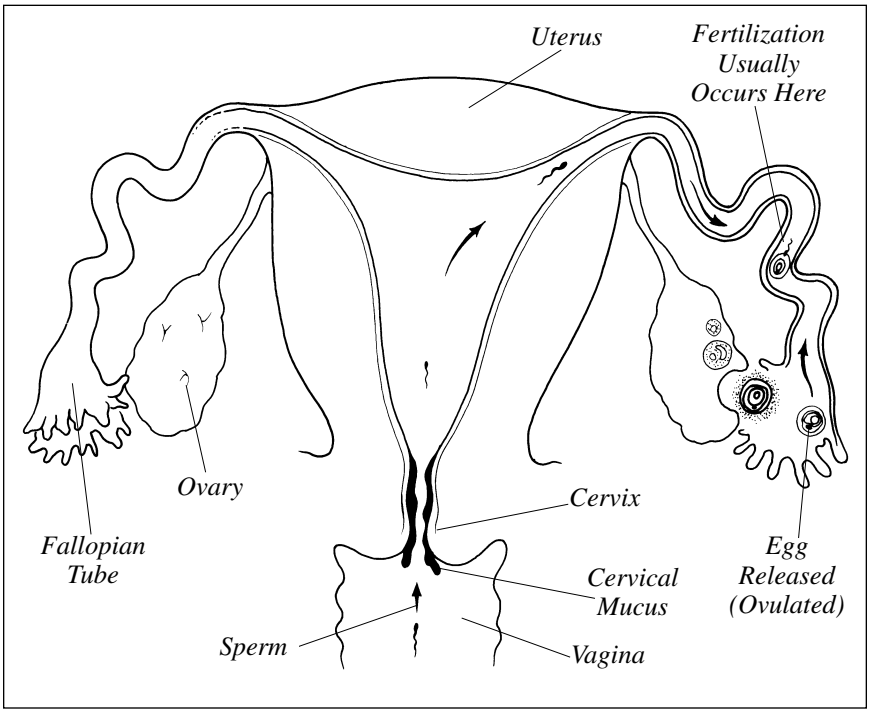

Figure 1. *Female reproductive tract.*

Hormone Production

In addition to producing eggs, the ovaries also secrete hormones. Hormones are substances secreted from organs of the body, such as the pituitary gland, adrenal gland, or ovaries, which are carried by a bodily fluid such as blood to other organs or tissues where the substances exert a specific action. The cycle of ovarian hormone production has two main phases. In the first phase, known as the *follicular phase*, an egg matures inside the ovary. The egg is

surrounded by a layer of hormone-producing cells and fluid. The maturing egg, the surrounding cells, and the fluid are collectively known as a *follicle*. The follicle grows to a diameter of about an inch, forming a cyst-like sac on the surface of the ovary, before the fluid and the egg are released at ovulation.

In natural cycles, an ovary contains several developing follicles, but usually only one follicle reaches maturity each month and releases an egg. This follicle, known as the dominant follicle, secretes a generous amount of the female hormone *estradiol* (*estrogen*) into the bloodstream during the first phase of the cycle. The estrogen circulates to the uterus where it stimulates the endometrial cells to reproduce rapidly and repeatedly, causing the uterine lining to thicken as ovulation approaches. The physician can usually see this thickening on an ultrasound exam.

The second phase of ovarian hormone production begins with ovulation. The dominant follicle ruptures, usually around day 14 in a 28-day cycle, and releases a mature egg onto the surface of the ovary near the fallopian tube. The empty follicle collapses and the remaining follicle cells develop a yellow color. Collectively these cells are known as the *corpus luteum*, literally a "yellow body." The corpus luteum secretes estrogen and large quantities of *progesterone* throughout the second half of the cycle, known as the *luteal phase,* which lasts approximately two weeks.

Traveling through the bloodstream to the uterus, the combination of progesterone and estrogen causes the uterine lining to further mature and produce nourishment for an embryo. About a week after ovulation, the endometrium is in prime condition for an embryo to implant. An experienced physician can tell approximately how many days have passed since ovulation by examining a sample of the endometrium taken in a *biopsy*. If no embryo implants, the secretion of estrogen and progesterone declines about two weeks after ovulation and, as a result, the endometrium is shed. This shedding of the endometrium is called menstruation.

The first day of menstruation is known as "cycle day one." The length of the menstrual cycle is determined by counting the number of days from cycle day one until the start of the next menstrual period. Although variability in cycle length is usually due to variability in the follicular phase, the luteal phase can also be variable in length. The luteal phase should last 11 to 16 days. If it is not sufficient in length because of inadequate progesterone production, fertility problems may result. Since ovulation usually precedes menstruation by two weeks, a woman with a 28-day menstrual cycle is most likely to ovulate on day 14. Similarly, a woman with a 32-day cycle is most likely to ovulate on day 18.

Directives From the Brain

The *hypothalamus* and *pituitary gland* orchestrate the events leading to ovulation. These organs communicate with the ovaries via hormonal messengers traveling in the bloodstream. The hypothalamus is a thumb-sized structure in the base of the brain that controls many bodily functions and regulates the pituitary gland. The pituitary gland, about the size of a finger tip, is located just beneath the hypothalamus. The hypothalamus releases the hormone *gonadotropin releasing hormone (GnRH)*, a messenger that tells the pituitary gland to release *follicle stimulating hormone (FSH)* and *luteinizing hormone (LH)*. FSH and LH are both involved in maturing the follicle, but FSH primarily makes the follicle grow and produce increasing amounts of estrogen. As the follicle grows, the increasing estrogen in the bloodstream signals the pituitary to shut down FSH production. A surge of LH triggers ovulation. After ovulation, the corpus luteum primarily produces progesterone, which prepares the endometrium for the implantation of a fertilized egg (Figure 2).

DIAGNOSIS

Detecting Ovulation

The key to diagnosing ovulatory problems is to detect and confirm ovulation. This can be done in several ways. An evaluation of the menstrual pattern provides some clues. A woman who menstruates every 25 to 35 days is probably ovulating regularly. She can also assume that ovulation occurs about 14 days before day one of each period. It is important to remember, however, that a woman can have randomly occurring uterine bleeding even though she never ovulates. Moreover, she can also have fairly regular cycles and not ovulate. There are several ways to detect ovulation, including commercially available ovulation prediction kits and basal body temperature charts. For more information on ways to detect ovulation, consult the ASRM patient information booklet titled *Ovulation Detection*.

TREATMENT: OVULATION MEDICATION

Who Needs Ovulation Medication?

Ovulation drugs are used to either control the time of ovulation or regulate erratic ovulation patterns. These medications, when administered appropriately, can stimulate ovulation in most individuals and can also correct post-ovulatory problems by encouraging more than one egg per cycle to reach maturity. If the time of ovulation is known, the doctor can schedule an *insemination*, for example, during the woman's "fertile days" to maximize the chance of pregnancy.

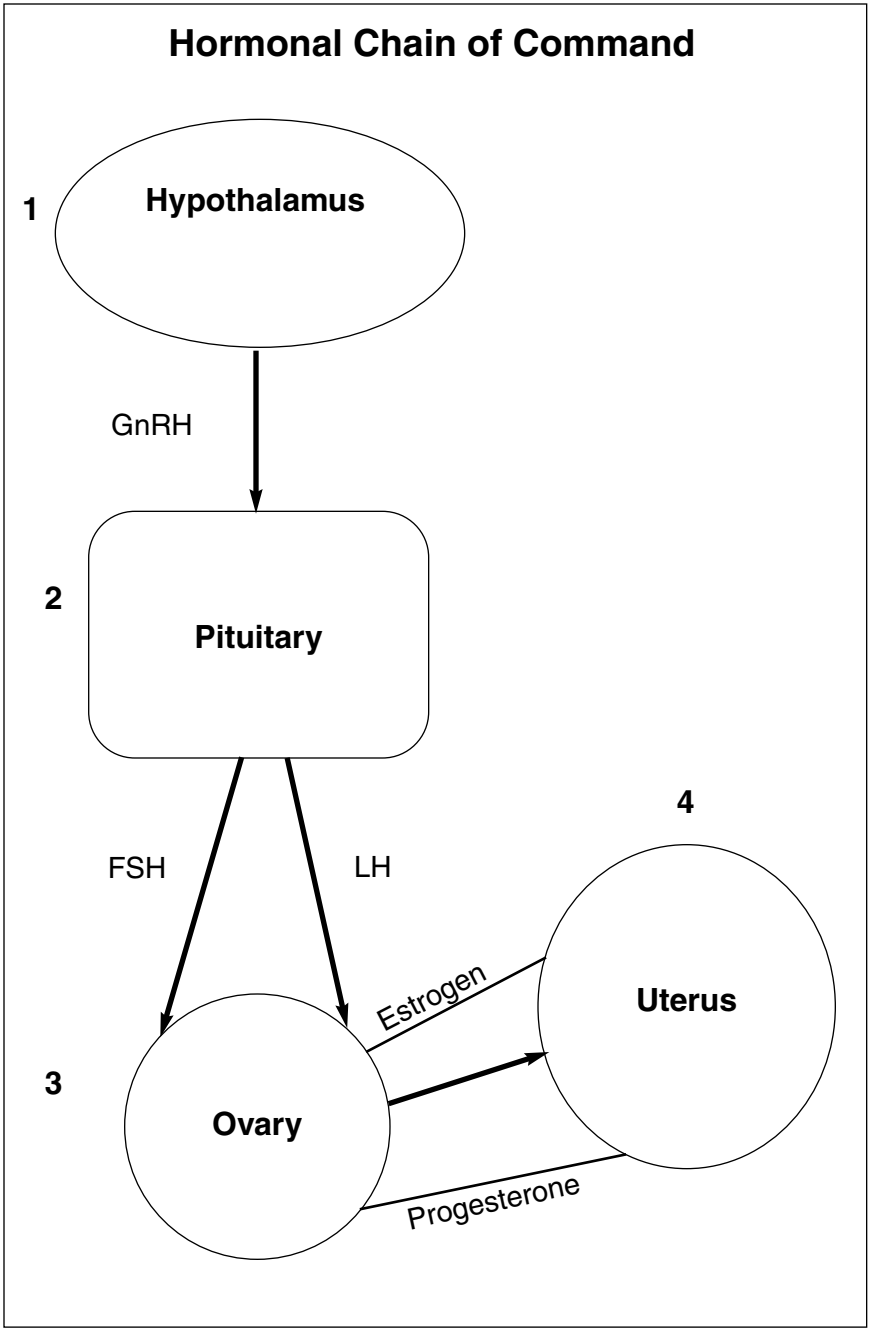

Figure 2. *Directives from the Brain.*

Ovulation drugs also may be prescribed to increase the reliability of monthly ovulation in *oligo-ovulatory* women (women who ovulate infrequently) or to encourage ovulation in anovulatory women. Women may not ovulate because of high ovarian production of male-type hormones (*polycystic ovarian syndrome [PCOS]*), insufficient production of LH and FSH by the pituitary, or ovaries that do not respond well to normal levels of LH and FSH. Ovulation drugs may be indicated in the treatment of women with *amenorrhea* (absence of menstruation) and may be used to temporarily correct a *luteal phase defect*.

A luteal phase defect occurs when progesterone production from the corpus luteum shuts down prematurely, produces an inadequate amount of progesterone to mature the uterine lining, or if the ovary did not actually release an egg at the normal time of ovulation. The interval of time between ovulation and the beginning of the next menstrual period is usually 11 to 16 days. If a luteal phase defect occurs, this time may be shortened and the endometrium won't be in the proper condition to receive and nourish an embryo; therefore implantation cannot occur. Ovulation drugs are used to correct a luteal phase defect by enhancing the production of progesterone from the corpus luteum after ovulation, thereby making the endometrium more optimal for embryo implantation. The endometrium also can be supported by the use of natural progesterone.

Ovulation drugs also can be used to encourage the ovaries to produce more than one egg per cycle. This is done in preparation for various forms of assisted reproduction such as intrauterine insemination or *in vitro fertilization (IVF)*. The intent is to develop several mature eggs in hopes that at least one egg will be fertilized and result in pregnancy. For more information on IVF, consult the ASRM patient information booklet entitled *IVF and GIFT: A Guide to Assisted Reproductive Technologies.*

An evaluation should be performed to look for hormonal imbalances before medication is administered to stimulate ovulation. Abnormal (inadequate) ovulation is sometimes caused by a hormonal imbalance resulting from other conditions, such as thyroid disease. Correction of imbalance may allow ovulation to resume spontaneously without the use of fertility drugs.

Commonly Prescribed Drugs

The most commonly prescribed ovulation drugs are *clomiphene citrate*, follicle stimulating hormone (FSH), *human chorionic gonadotropin* (*hCG*), and *human menopausal gonadotropin (hMG)*. These and four others, *bromocriptine*, *cabergoline*, gonadotropin releasing hormone (GnRH), and *GnRH analogs,* which have very specialized applications, are described below. A chart is provided listing these ovulation drugs and their side-effects (Figure 3).

Drugs Used for Ovulation Induction

Generic Name	Brand Name(s)	Form	Most Common Side Effects
Clomiphene citrate	Clomid® Serophene®	Tablets	• increased incidence of multiple births, miscarriage • thick, dry cervical mucus • hot flashes, nausea, breast tenderness • occasional headaches or blurred vision • depression, mood swings • ovarian cysts, pelvic discomfort
Follicle Stimulating Hormone (FSH)	Fertinex™ Follistim™ Gonal-F®	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)
Human Chorionic Gonadotropin (hCG)	A.P.L.® Pregnyl® Profasi®	Injection	• no known side-effects if only taking hCG
Human Menopausal Gonadotropin (hMG)	Humegon™ Pergonal® Repronex™	Injection	• same as for FSH
Bromocriptine Cabergoline	Parlodel® Dostinex™	Capsules Tablets	• nausea, vomiting, nasal congestion • headache, dizziness, fainting • decreased blood pressure
Gonadotropin-Releasing Hormone (GnRH)	Factrel® Lutrepulse®	Injection	• slight chance of multiple births, mild hyperstimulation syndrome • headache • nausea
GnRH Analogs	Lupron® (Leuprolide Acetate) Synarel® (Nafarelin Acetate) Zoladex® (Goserelin Acetate)	Injection Nasal Spray Injection	• hot flashes, headache • mood swings, insomnia • vaginal dryness • decreased breast size • painful intercourse • bone loss
GnRH Antagonists	Antagon™ (Ganirelix Acetate)	Injection	• same as GnRH Analogs

Figure 3. *Ovulation drugs, their brand names, and most common side effects.*

Clomiphene Citrate

The generic name of the most commonly prescribed ovulation drug is clomiphene citrate. Brand names include Clomid® and Serophene®. This drug is most often used to stimulate ovulation in women who have infrequent periods and long cycles. The standard dosage is one to two tablets (50 to 100 milligrams) per day for five consecutive days. The regimen begins early in the cycle, usually on the second, third, fourth, or fifth day after menstruation begins. If necessary, a menstrual period can be induced by *progestin* tablets or by an injection of natural progesterone before clomiphene therapy is started. The physician may first do a pregnancy test before administering progestin or progesterone. Provera®, Cycrin®, and Amen® are forms of medroxyprogesterone acetate, the progestin most commonly used to bring on menstrual bleeding. Vaginal progesterone (Crinone™) or progesterone pills (Prometrium®) also may be prescribed. These medications should not be used unless the physician is sure that the woman is not pregnant.

Clomiphene works by blocking estrogen receptors in the hypothalamus, causing it to "think" there is an estrogen deficiency in the bloodstream. As a result, the hypothalamus orders the pituitary gland to secrete more FSH and LH into the bloodstream. The high level of FSH spurs the development of a follicle and its egg. As the follicle grows, it secretes estrogen into the bloodstream. About a week after the last clomiphene tablet is taken, the hypothalamus senses the increased estrogen level and signals the pituitary to release a surge of LH. This LH surge causes the egg to be released from the mature follicle in a process called ovulation.

If treatment is successful, ovulation usually occurs about a week or so after the last clomiphene tablet has been taken (from day 12 through day 21 of the cycle). The total cycle may be as long as 35 days. Most doctors rely on the menstrual pattern, the basal body temperature (BBT) chart, ovulation prediction kits, or serum progesterone levels 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 four-tenths of one degree or more. If these ovulation tests are positive, generally no other drugs are needed. If there is doubt, however, measuring the progesterone level about 18 to 21 days after the start of clomiphene, or using *ultrasound* monitoring, can help to determine if and when ovulation occurred. If ovulation does not occur, the clomiphene dose may be increased in the next few cycles. If the larger dose of clomiphene fails to cause ovulation, the physician may choose to prolong the duration of treatment. 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 information booklet titled *Ovulation Detection*.

Clomiphene can alter the quality of *cervical mucus*, making it a thick, dry, and an impassable barrier for sperm. Some physicians may recommend a *postcoital test* during a cycle of clomiphene therapy. For this test, the couple is asked to have intercourse during the time ovulation is predicted to occur. Soon afterward (usually four to 12 hours), in the doctor's office, a sample of the woman's cervical mucus is removed and examined under a microscope to see if sperm are present and able to move in the mucus. If the test is unsatisfactory, the physician may prescribe treatment to restore the proper consistency of the cervical mucus, or may perform an intrauterine insemination to bypass the *cervix*. Sometimes a change in medication to hMG or FSH may be the most appropriate action.

Clomiphene can sometimes alter endometrial thickness, making it thin and unreceptive to implantation. If this occurs, the physician may prescribe medication to increase the thickness of the endometrium, or change the prescribed medication to hMG or FSH.

Many doctors prescribe clomiphene to treat luteal phase defects. However, a luteal phase defect is also a possible side effect of clomiphene therapy. This problem can usually be corrected by adjusting the dosage with each cycle or by supplementing it with progesterone after ovulation until adequate endometrial development is achieved.

The lowest dose of clomiphene sufficient to induce ovulation is usually used for at least four to six cycles to provide an adequate trial for most patients. About 40 to 45 percent of couples receiving clomiphene citrate will become pregnant after six cycles. Most authorities suggest that clomiphene be given for no more than six cycles prior to considering alternatives. 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.

Human Chorionic Gonadotropin

A.P.L.®, Pregnyl®, and Profasi® are brand names for human chorionic gonadotropin (hCG). Sometimes hCG is added to the clomiphene regimen. Like a woman's natural LH surge, hCG causes the dominant follicle to release its egg. Produced by the placenta during pregnancy and extracted from the urine of pregnant women, hCG is similar in chemical structure and function to LH. The physician may use ultrasound images and blood estrogen levels to determine the precise day on which to administer hCG. Ovulation will usually occur 36 to 72 hours after hCG is administered. An early pregnancy test may be falsely positive if performed less than 10 days

after hCG is administered. If the patient still does not ovulate after hCG, she may become a candidate for hMG or FSH.

Human Menopausal Gonadotropin

Humegon™, Repronex™, and Pergonal® are brand names for human menopausal gonadotropin (hMG), one of the most potent ovulation drugs currently in use. It is given by injection and contains equal parts of FSH and LH (or hCG as an LH substitute), which are derived from the urine of postmenopausal women. FSH and LH have a direct impact on the ovaries by stimulating them to produce multiple eggs in one cycle.

The hMG is often prescribed for anovulatory women who have tried clomiphene without success. It may also help women whose pituitary glands do not produce adequate amounts of FSH and LH and as a result do not have menstrual periods (amenorrhea). In addition, this drug is used for IVF and other assisted reproductive technologies to help produce multiple eggs. Although younger women tend to produce more eggs than older women, each woman will respond differently. Many physicians will obtain a blood test for FSH on day two or three of the cycle in order to better predict how the ovary will respond to hMG. If the FSH level on day two or three of the cycle is elevated, then a poor response to these medications can be predicted. Under these circumstances, alternatives involving other methods of assisted reproduction may be discussed.

HMG treatment involves a series of injections and careful monitoring during each treatment cycle. Because this may involve a certain amount of risk, expense, and inconvenience, many physicians first recommend a complete infertility work up including a *laparoscopy*. 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, approximately 20 percent to 30 percent per treatment cycle.

Most physicians begin hMG treatment on day two or three of the menstrual cycle. The usual starting dose is one or two *ampules* (75 to 150 units) injected daily. Injections are usually administered over a period of seven to 12 days, but this period 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 hMG, 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 or a high-order multiple pregnancy.

Follicle Stimulating Hormone

Fertinex™, Gonal-F™, and Follistim™ are the brand names for FSH. FSH was initially purified from the urine of postmenopausal women. Fertinex™, is derived from the urine of postmenopausal women. Fertinex™ can be given by a subcutaneous injection (immediately beneath the skin). Fertinex™ is similar to hMG except that almost all of the LH has been removed. Recently, purified synthetic FSH has been developed through sophisticated manufacturing techniques and is now sold under the brand names of Gonal-F™ and Follistim™. These products contain no LH at all. They're also administered via subcutaneous injection. Like hMG, these FSH medications bypass the hypothalamus and pituitary and directly stimulate follicular growth in the ovary.

Most women who try FSH have already used clomiphene therapy without success. Many of these women have an elevated LH level and a low to normal FSH level. This combination is characteristic of polycystic ovarian syndrome (PCOS), a common diagnosis in women with ovulation problems. FSH is often added to hMG when the initial response to that drug is inadequate. For more information on PCOS, refer to the ASRM patient information booklet titled *Polycystic Ovarian Syndrome*.

Bromocriptine and Cabergoline

Some women ovulate irregularly because their pituitary glands secrete too much *prolactin*, the hormone that stimulates breast milk production in new mothers. Increased blood levels of prolactin may stop the normal ovulatory cycle because prolactin inhibits the release of FSH and LH. This condition is often 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.

There are several causes of elevated prolactin levels in nonpregnant women. Excess prolactin may result from a cluster of cells within the pituitary gland that form a type of benign (non-cancerous) pituitary tumor called an *adenoma*. Even very small adenomas can be detected and their size measured by modern imaging techniques such as the CAT scan (computed axial tomography) or MRI (magnetic resonance imaging). Bromocriptine and cabergoline may shrink the adenoma and lower the blood level of prolactin to normal. Continued use of the drug, often only a small dose, is necessary to maintain a normal prolactin level in patients with adenomas.

The prolactin level is elevated in some women because the prolactin-producing cells in the pituitary are hyperactive. High prolactin levels can also 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.

These medications suppress prolactin production, and the blood prolactin level returns to normal in more than 90 percent of cases. Bromocriptine is orally taken 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 percent 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.

Gonadotropin-Releasing Hormone

Factrel® and Lutrepulse® are brand names of 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 by a special drug delivery system that includes a belt holding a lightweight pump. At intervals of about 90 minutes, the pump delivers a small volume of fluid through a needle placed beneath the skin (usually in the abdomen) or into a blood vessel.

Gonadotropin-Releasing Hormone Analogs (Agonists and Antagonists)

GnRH analogs are synthetic hormones similar to GnRH, but they act in a very different manner. Several drugs of this type are currently available in the United States: Lupron® (leuprolide acetate), Synarel® (nafarelin acetate), and Zoladex® (goserelin acetate) are GnRH agonists. Antagon™ (ganirelix acetate), is a pure *GnRH antagonist*. Others are under study or in use in other countries. These drugs, which are ineffective when taken orally, are prescribed as a daily, monthly, or quarterly injection, or a nasal spray.

The rhythmic release of GnRH 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. GnRH agonists are prescribed for some patients with abnormal ovulatory cycles to enable them to respond better to hMG. By preventing communication between the pituitary gland and the ovaries, GnRH agonists

allow the gonadotropin injections to be the sole source of follicle stimulation. Some physicians use agonists to induce ovulation and prevent the pituitary from prematurely creating the LH surge. A premature LH surge often results in cancellation of a cycle of ovulation induction for IVF or GIFT. The GnRH antagonists cause LH and FSH to be immediately suppressed.

In IVF and GIFT programs, a GnRH agonist is often used to prevent spontaneous ovulation when gonadotropins are given. 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.

GnRH agonists have also been shown to help stimulate ovulation when given at midcycle and the ovarian follicles are mature.

RISKS AND COMPLICATIONS OF OVULATION DRUGS

There are potential risks and complications associated with the use of ovulation drugs. Side-effects should be discussed prior to taking ovulation drugs.

Women taking clomiphene have up to a 10 percent chance of having twins. The likelihood of having more than two babies is less than 1 percent. There is a slightly 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 mild to moderate overstimulation of the ovaries. A pelvic exam or ultrasound may be performed to look for ovarian cysts before beginning another clomiphene treatment cycle. Other side-effects of clomiphene may include hot flashes and mood swings while taking the drug, followed by depression, nausea, and breast tenderness. Mood swings may be surprising, severe, and persist throughout a treatment cycle. As previously mentioned, a luteal phase defect may also occur. Side-effects are more frequent with higher doses. Severe headaches or visual problems, which are rare, are signs to stop treatment immediately and call the physician.

Despite intensive monitoring, multiple pregnancies occur in approximately 25 percent of gonadotropin cycles. 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 present in the uterus, the greater the risk of premature delivery. Premature delivery subjects the newborn to many complications including 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. 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. The most serious side-effect is *ovarian hyperstimulation syndrome*, in which the ovaries become swollen and painful. In severe cases, fluid accumulates in the abdominal cavity and chest. In about 2 percent of cases, hyperstimulation requires hospitalization. Fortunately, hyperstimulation rarely occurs without ovulation. Because most gonadotropin-treated patients need an hCG injection to trigger ovulation, the physician may choose to withhold the injection to decrease the chance of severe hyperstimulation or multiple births, if tests show that the patient's estrogen level is too high or if too many follicles are present. 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.

Possible side effects of bromocriptine and cabergoline include nasal congestion, fatigue, drowsiness, headaches, nausea, vomiting, fainting, dizziness, and decreased blood pressure. For most patients, these side-effects can be eliminated by adjusting the dosage. 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.

The risk and complications of GnRH, such as multiple births and ovarian hyperstimulation syndrome, are quite small. The patient taking a GnRH antagonist or agonist 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.

LONG-TERM RISKS OF OVULATION DRUGS

After years of clinical use, physicians can confidently advise patients that ovulation drugs are not associated with an increased risk of birth defects. Recently, several studies have suggested that women taking ovulation-inducing drugs such as clomiphene and gonadotropin may be at increased risk for ovarian cancer. Although the data suggest that infertile women, and in particular women who take infertility medications, have a higher risk of ovarian cancer, it is not known whether or not the drugs are the cause of the

increased risk. In fact, in one well-known study, the achievement of pregnancy with or without the use of infertility drugs was associated with decreased ovarian cancer risk. Even though one study implicated long-term clomiphene use in an increase in ovarian cancer rates, it is not completely certain at this time which fertility drugs, if any, might increase the risks. Most studies relative to gonadotropin use do not reveal any increased risk for ovarian cancer. Clearly, more research needs to be conducted to address these issues. In the meantime, it is important that women taking these medications discuss the risks with their physicians. One must weigh the unproven risks against the clear benefits of ovulation-inducing agents.

Conclusion

Not all infertile women are candidates for ovulation drugs. To determine the need for ovulation drugs, physicians require patients to undergo a series of tests to identify the presence and exact cause of the ovulation problem. Once a diagnosis is made, it may take several cycles (months) to determine the right medication and dosage to trigger ovulation. An anovulatory woman should be prepared to visit her doctor frequently for ultrasound tests, blood tests, and other monitoring procedures. Sexual intercourse may have to be carefully timed. The regulation of ovulation requires an investment of time, money, energy, and emotion. While most cycles end with disappointment because a pregnancy is not achieved, all the effort is justified for couples because the majority ultimately give birth to a healthy baby.

Glossary

Adenoma. A type of benign (non-cancerous) pituitary tumor which may secrete excess amounts of prolactin or other hormones.
Amenorrhea. Absence of menstrual periods.
Ampules. Sealed vials containing a sterile medicinal solution usually injected intravenously or intramuscularly.
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.
Cervical mucus. A thick, stringy substance produced by cervical glands under the influence of estrogen stimulation.
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.

Corpus luteum. A hormone-producing structure that develops in the ovary from a follicle which has released 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 which 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.

Follicle. A fluid-filled, cyst-like structure just beneath the ovary's surface in which the egg grows to maturity.

Follicle-stimulating hormone (FSH). The pituitary hormone responsible for the stimulation of estrogen production from the follicle cells around the egg. Fertinex™, Gonal-F™, and Follistim™ are brand names.

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). A hormone secreted by the hypothalamus that prompts the pituitary gland to release follicle stimulating hormone and luteinizing hormone into the blood stream. Factrel® and Lutrepulse® are brand names.

GnRH agonists. Synthetic hormones similar to the naturally occurring gonadotropin-releasing hormone (GnRH) which initially stimulate and then subsequently decrease FSH and LH secretion from the pituitary gland Lupron®, Zoladex®, and Synarel® are brand names.

GnRH antagonists. Synthetic hormones similar to the naturally occurring gonadotropin-releasing hormone (GnRH) which block the physiological action of GnRH.

Human chorionic gonadotropin (hCG). A hormone produced by the placenta during pregnancy that is often used with clomiphene or hMG to cause ovulation. A.P.L.®, Pregnyl®, and Profasi® are brand names.

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

Humegon™ are brand names.

Hypothalamus. A thumb-sized area in the base of the brain that controls many body functions and regulates the pituitary gland.

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.

Laparoscopy. The insertion of a long, thin, lighted telescope-like instrument called a laparoscope through an incision into the abdomen to look for abnormalities of the internal reproductive organs and in some cases to surgically correct these abnormalities.

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. 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.

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 in which the ovaries have many cystic follicles, presumably because the eggs are not expelled. Symptoms may include irregular or absent menstrual periods, obesity, excessive hair growth, and/or acne.

Postcoital test. An examination of a woman's cervical mucus after she has had intercourse to determine the number and motility (ability to move) of

sperm in the mucus.

Progesterone. An ovarian hormone secreted by the corpus luteum during the second half of the menstrual cycle. Progesterone helps prepare the endometrium to receive and nourish an embryo.

Progestin. A synthetic hormone that acts similar to progesterone.

Prolactin. A pituitary hormone that stimulates milk production.

Ultrasound. High frequency sound waves that produce an image on a monitor screen of internal organs.

Uterus. A hollow muscular organ in which the fetus develops during pregnancy.

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