

Fertility Perspectives



GLENN P. PALMISANO, M.D.

A NEWSLETTER FOR PEOPLE WITH CONCERNS ABOUT INFERTILITY

NEW DEVELOPMENTS IN OVULATION INDUCTION

*O*vulation induction is used as part of fertility treatment in a variety of therapies, and it increases the chance of pregnancy in many types of fertility problems. The treatment involves the use of fertility drugs, carefully monitored, as needed, with ultrasound and blood tests, to stimulate the ovaries to produce multiple healthy eggs. Research on and development of new fertility medications will continue to expand the options for successful fertility treatment in the future.

Ovulation induction is used for two groups of couples. In the first group are women who have obvious ovulation defects: abnormal ovulatory cycles, no menstrual periods, or only two or three periods a year. The second group includes all those couples who do not have obvious ovulation problems but are being treated for unexplained infertility or other infertility problems—provided that the woman has at least one normal fallopian tube. This second group now encompasses all couples except those in which the husband has severe male factor infertility or the woman has severely damaged tubes and ovaries. Couples in the second group may have mild endometriosis, cervical factor, mild tubal disease, mild sperm problems, or fertility problems related to age. This group accounts for the majority of cases where ovulation induction is used.

The goal of treatment with known ovulation problems is to correct the defects. On the other hand, the goal of treatment in the “unexplained” group is to augment fertility and also to correct any subclinical, or hard to detect, ovulation defects.

Ovulation induction is part of the treatment in clomiphene therapy plus IUI (intrauterine insemination) as well as gonadotropin therapy plus IUI (see below). The assisted reproductive

technologies, IVF, GIFT, and ZIFT, generally combine the use of GnRH agonists (these remove control of ovulation from the pituitary gland) and a combination of ovulation-induction medications that act directly on the ovaries to produce multiple eggs. Recruitment of multiple eggs increases the chance that a woman will have a successful pregnancy.

THE DRUGS THAT DO THE WORK

Gonadotropic hormones play a key role in regulating the menstrual cycle; they are also very important fertility drugs. An overview of the hormones that govern the menstrual cycle helps to explain in part how the ovulation-induction medications work.

The brain's pituitary gland produces what are known as gonadotropic hormones—follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These circulate through the bloodstream and stimulate the ovaries to cause the maturation of follicles that produce eggs at midcycle. In nature, generally just one egg is produced. In ovulation induction, multiple follicles may mature and produce eggs.

Clomiphene citrate (Clomid, Serophene) is one of the oldest and least expensive fertility drugs. It is still commonly used as a first step for ovulation induction in many programs. Clomiphene acts on the pituitary gland to increase the production of gonadotropic hormones. Clomiphene can be taken by mouth. The cost is considerably lower than that of the gonadotropic hormones; however, it is not always as effective.

Gonadotropic hormones, FSH and/or LH, act directly on the ovaries. They are administered by injection. If taken by mouth, they would be rapidly destroyed by the stomach. Except in cases of women who are menopausal or who have ovarian failure, the gonadotropic hormones rarely fail to induce ovulation.

SPRING 1997

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Pergonal and Humegon are gonadotropic hormones made up of FSH and LH. Metrodin is just FSH. A new medication called Fertinex has just become available in the US. It is made from a highly purified form of FSH. Fertinex can be given subcutaneously with a small needle, instead of into a muscle (IM). It may be less painful for the patient than an IM injection, and is easier for her to do herself.

The next breakthrough in drug technology, which pharmaceutical companies are working on, will be “recombinant” forms of FSH and LH, based on extensive research and genetic engineering. Currently, the gonadotropic-hormone medications are what are called urinary products. The actual hormones are extracted from the urine of postmenopausal women. Urinary products may vary slightly in potency from one batch to another. The new, recombinant products will be synthetic. They will be manufactured in the laboratory and will be much purer and more standardized. Because the drugs will be in a very concentrated form, patients will be able

to administer the subcutaneous injections themselves. Many experts predict that eventually most of the drugs used in fertility treatment will be recombinant products, synthesized in the laboratory.

The GnRH agonists have been in use for a long time to treat a wide range of problems. Lupron, Synarel, and Zoladex are synthetic compounds that act on the pituitary gland to interrupt production of FSH and LH. Left to its own devices, the pituitary gland attempts to limit the number of eggs produced to only one or two. GnRH agonists serve to sidestep the pituitary's control of ovulation. Then gonadotropic hormones are given to stimulate the ovaries directly, without any interference from the pituitary gland. Most IVF programs use this treatment protocol in order to produce a larger number of mature eggs for fertilization. Some women who experience difficult ovulation problems—for example, women with polycystic ovary syndrome—may ovulate more successfully if they are first given GnRH agonists and then fertility medications.

Two other medications, called dexamethasone and bromocriptine, are also sometimes used as adjuncts to

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LUTEAL PHASE DEFECTS IN INFERTILITY

The corpus luteum, the capsule that remains after the release of the egg, or ovum, from the follicle each month, gives its name to the second half of the menstrual cycle. The corpus luteum acts like a small hormone factory; it produces the estrogen and progesterone that maintain the uterine lining until either a pregnancy or a menstrual period occurs. The luteal phase is the time between ovulation and the beginning of menses. Over 50 years ago, a fertility deficiency called a luteal phase defect was first described. This disorder may consist of a deficiency of progesterone production or an inadequate development of the uterine lining (endometrium), and can cause infertility or repeated early pregnancy

loss. Today, even though scientists can't always specify what causes the defect and continue to debate about how exactly to measure it, it can often be successfully treated using modern fertility drugs.

Historically, luteal phase defects were diagnosed using a combination of basal body temperature charts, hormone blood tests, endometrial biopsies, and ovulation prediction kits. A woman with a luteal phase shorter than 10 days was suspected of having a luteal phase defect. Likewise, a low blood level of progesterone a week after ovulation indicated a possible luteal phase defect. Another diagnostic tool was an endometrial biopsy, where a sample of the lining of the uterus was taken a few days before the menstrual period, then specific criteria about endometrial dating were applied. The

appearance of the cells from the uterine lining would indicate whether a woman was in or out of phase in that cycle. Treatment has traditionally been with progesterone or with a variety of ovulation-induction medications.

One of the reasons that luteal phase defects get less press these days is that modern medical science, in many cases, can treat the problem more effectively than it can define or diagnose it. Most women—as long as they have open fallopian tubes and their husbands have acceptable sperm counts—are now being placed on treatment regimens that involve using ovulation-induction medications. Usually these treatments are quite effective. It has become less important to specifically identify luteal phase defects, because today's broad-spectrum treatments correct this problem so effectively. ☼

therapy in ovulation-induction programs (see Glossary, this page).

CAREFUL MONITORING ENHANCES THE SAFETY OF OVULATION INDUCTION

Ovulation induction with gonadotropins is always carried out in conjunction with close monitoring by vaginal ultrasound exams and estrogen blood tests. The purpose of this surveillance is to help pinpoint ovulation as well as to safeguard against the development of too many eggs or overstimulation of the ovaries. Ovulation induction carries some risks; the principle concerns are multiple pregnancy and ovarian hyperstimulation syndrome. The majority of multiple gestations will result in twins; however, triplets or more can occur. Although ovarian hyperstimulation syndrome is very rare, it can potentially be serious and may result in hospitalization.

Advances in the field of ovulation induction can in large part be traced to the wealth of research related to IVF and GIFT. This research has allowed scientists to scrutinize all phases of ovulation induction. Although the majority of infertile couples will not need to resort to IVF or GIFT, they may well reap the benefits of what has been learned from these programs. In addition, the new, recombinant forms of fertility medications that are on the horizon will be easier to administer and will be more standardized. ☞

GLOSSARY OF COMMONLY USED FERTILITY DRUGS

Many different medications are used in infertility treatment. Developments in the field of pharmacology deserve credit for much of the success in overcoming infertility over the past 25 years. Some drugs (ovulation-induction medications) are specifically used to stimulate or fine-tune the functioning of the ovaries. Others correct hormonal defects or are used along with ovulation-induction medications.

CLOMIPHENE CITRATE (brand names: Clomid, Serophene) is a long-standing, first-line-of-treatment drug used for ovulation induction. It is an estrogen-like synthetic hormone that acts upon the pituitary gland to activate secretion of gonadotropic hormones (FSH and LH). These hormones then stimulate the ovaries.

DEXAMETHASONE (Decadron and several other brands) may be added to clomiphene therapy in some cases to increase ovulation and conception rates. It acts by lowering elevated levels of male hormones (androgens).

FERTINEX is the newest fertility drug available. It consists of purified FSH (follicle-stimulating hormone), one of the pituitary gonadotropic hormones. Administration is subcutaneous or by IM injection.

GnRH AGONISTS (brand names: Lupron, Synarel, Zoladex) suppress the pituitary gland's control of ovarian function. They are used in many IVF programs in conjunction with Pergonal, Humegon, Metrodin, and/or Fertinex.

HUMEGON AND PERGONAL are different brand names for the same drug, which consists of a mixture of the pituitary gonadotropic hormones LH (luteinizing hormone) and FSH (follicle-stimulating hormone). Administration of the drug is by injection into a muscle.

HCG (human chorionic gonadotropin) is given as an injection at midcycle, to mimic the effect of the body's own hormone LH, which triggers the release of the egg. HCG is part of the protocol in IVF and GIFT programs. It is also used in many other ovulation-induction protocols.

METRODIN is a pituitary gonadotropic hormone made up of just FSH (follicle-stimulating hormone). It is given by injection into a muscle.

PARLODEL (bromocriptine) is used to bring high levels of the hormone prolactin back down to normal. Prolactin is secreted by the pituitary gland and regulates lactation (breast feeding). Elevated prolactin levels can interfere with ovarian function. Parlodel inhibits the pituitary secretion of prolactin.

PROGESTERONE is a naturally occurring hormone, which is produced by the corpus luteum in normal ovulatory cycles. It is given to treat luteal phase defects and to support the uterine lining in many ovulation-induction programs.



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SURVIVING INFERTILITY

Infertility treatment can work wonders. For many couples, though, the challenge is how to survive infertility treatment as well as how to succeed at it. Persistence and perspective are key factors. Everyone with infertility experiences stress in treatment. The following list of suggestions may prove helpful to couples coping with infertility.

- Educate yourself. Ask your doctor for any written information about the treatments you receive and about medications you take. Then take the time to do some reading on infertility.
- Find out what the odds of success are with a particular medication or treatment and be realistic about your chances of conceiving.
- Set short-term goals. For example, pursue your treatment one step at a time. Don't waste energy worrying about what you will do next.
- Be organized. Know in advance what questions you want answered at your next visit. Write down your questions or concerns as you think of them. If you feel you need more time to talk, ask your doctor to schedule a visit just to consult.
- Develop a budget for infertility treatment. Figure out how much you can afford to spend on your treatment, and then make plans accordingly.
- Keep your infertility treatment in perspective. Set aside times for appointments and time for reading. At other times, try to put the subject of infertility out of your mind.
- Focus on wellness. Eat well and exercise. Get enough sleep.
- Have fun and keep busy. Try to maintain your sense of humor. Make your life as full as possible. If you have the time, doing some volunteer work may help you to focus less on your own problems.
- If you are feeling depressed, angry, confused, or resentful, you might want to see a trained counselor. Discuss these concerns with your doctor.
- Join an infertility support group or find a friend that you can talk to about infertility. ☺



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Fertility Perspectives published by

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Fertility Perspectives is published by Glenn P. Palmisano, M.D. The goal of this newsletter is to provide medical information on infertility. The contents are not intended to provide personal medical advice, which should be obtained from a physician.