

## GONADOTROPIN STIMULATION FACT SHEET

This is a brief description of the various injectable medications used for Ovulation Induction (OI), Controlled Ovarian Hyperstimulation (COH) and in vitro fertilization (IVF). Not all patients will be using all of the medications or procedures described here.

### Human Menopausal Gonadotropins, hMG (Repronex, Pergonal, Bravelle)

The term "gonadotropins" refers to the hormones FSH (Follicle Stimulating Hormone) and LH (Luteinizing Hormone). These purified hormones have been available as an injectable medication since the 1960's. "HMG" stands for "Human Menopausal Gonadotropins" and refers to preparations of gonadotropins that are produced by isolating and purifying these hormones from the urine of post-menopausal women. FSH and LH are similar proteins so they are difficult to separate from each other. FSH and LH are present in these preparations in approximately equal amounts. Despite rigorous purification, there remain small amounts of urinary proteins in HMG preparations. There are no known cases of disease being transmitted from one person to another through these medications.

### RECOMBINANT FSH, rFSH (GONAL-F, FOLLISTIM)

This gonadotropin is produced in the laboratory using recombinant DNA technology. Because FSH is a large and complex molecule, it is difficult to synthesize in the laboratory and has only been available since 1992. Recombinant FSH is a pure preparation of FSH and contains virtually no LH. It is possible to synthesize pure LH as well and while it is currently available in Europe, it is not yet available in the U.S. for clinical use.

### HUMAN CHORIONIC GONADOTROPIN, hCG (OVIDREL, NOVAREL, PREGNYL)

Chorionic gonadotropin is a hormone produced by the developing placenta that closely resembles LH. hCG (human chorionic gonadotropin) is available as an injectable medication that is used clinically to produce LH effects. Urinary hCG (uhCG) is produced by isolating and purifying the hormone from the urine of pregnant women. Recombinant hCG (rhCG) is synthesized in the laboratory using recombinant DNA technology. Urinary hCG preparations, like hMG, contain small amounts of urinary proteins. There are no known cases of disease being transmitted of one person to another through these medications.

hCG is used primarily to simulate an LH surge in order to trigger the final steps of oocyte maturation and ovulation in women attempting to conceive.

### ROUTE OF ADMINISTRATION

Recombinant FSH (rFSH) and hCG (rhCG) are given subcutaneously using a very small needle. hMG and urinary hCG may be administered either subcutaneously or intramuscularly. Because it is much easier to give a subcutaneous injection, this is the preferred route for all these medications.

### SIDE EFFECTS

With any of these injections, it is possible to have pain, rash, or swelling at the injection site. When given subcutaneously, hMG and urinary hCG may cause more local swelling, redness or irritation.

Other possible side effects include:

- Abdominal or pelvic pressure or pain
- Bloating
- Nausea and vomiting
- Breast swelling and tenderness
- Mood changes
- Fluid retention and weight gain

Other side effects, including allergic reactions, have been reported but with an incidence of less than 1%

### RISKS

There are two main risks resulting from the use of gonadotropins to stimulate the ovaries. These include:

- Multiple pregnancy
- Ovarian hyperstimulation syndrome

### MULTIPLE PREGNANCY

As a result of stimulating the ovaries with FSH, the normal mechanism that limits the number of eggs released from the ovary in a given cycle is overridden. Thus, multiple eggs may develop and be available for fertilization and implantation. Indeed, this is one of the benefits of treatment with gonadotropins and confers its utility. But, it also increases the risk for multiple gestations. To safely use this method for conception, we must manage the stimulation to maximize benefit but minimize risk. Even with careful monitoring, it is not possible to eliminate the risk for multiple pregnancy. With IVF, we can stimulate more vigorously because not all of the embryos produced need be transferred in one cycle. With OI and COH, all the eggs that



are ovulated are potentially available for fertilization and implantation. In a natural cycle, the probability that a pregnancy will be multiple is about 3%. After clomiphene treatment, it is about 7%. After OI and COH with gonadotropins, the probability is close to 20%. Of these, 75% are twin gestations but higher order multiple pregnancy (triplet, quadruplet, quintuplet...) make up the remaining 25% unless the clinic employs careful monitoring. With careful monitoring the rate of HOMP should be 5-7%. In IVF treatment, the multiple pregnancy rate is determined by the number of embryos that are transferred into the uterus at one time. The published rates range from 10% to 30%.

### **OVARIAN HYPERSTIMULATION SYNDROME**

Ovarian Hyperstimulation Syndrome, or "OHSS", is a medical complication that can occur as the result of the use of gonadotropins. OHSS is rarely seen after the use of clomiphene; the estimated incidence is less than 1%. But, OHSS may occur in up to 8% of women using gonadotropins for ovarian stimulation for IVF. The clinical spectrum of this syndrome is broad and most affected women have only a mild to moderate form. Severe OHSS occurs in 0.1-2% of IVF cases and less frequently in ovulation induction treatment cycles. In its severe form, OHSS is characterized by ovarian enlargement, a large accumulation of fluid in the abdomen (ascites) with hemoconcentration and reduced urine output. Blood electrolytes are often abnormal. Kidney and liver function may be impaired and there is an increased risk for blood clots. Severe OHSS is a rare but serious complication that may require hospitalization. See separate fact sheet.

### **MISCARRIAGE, STILLBIRTH, AND FETAL CONGENITAL MALFORMATIONS (BIRTH DEFECTS)**

Studies have not shown any increase in miscarriage, stillbirth or congenital anomalies as a result of the use of gonadotropins.

### **CANCER**

Gonadotropins have been implicated as a risk factor for ovarian cancer but more recent studies suggest that the risk may be from infertility itself rather than the medications used to treat it. Successful pregnancy reduces the risk of ovarian cancer considerably. It remains uncertain whether these medications carry any long term risk.

There appears to be no increased risk of breast cancer associated with use of these medications.

### **Gonadotropin releasing hormone agonist - GnRHa (Lupron, Synarel)**

GnRH agonists are synthetic protein derivatives of the human hypothalamic hormone GnRH. They are administered by injection (Lupron) or inhalation (Synarel). When given continuously at therapeutic doses, GnRH agonists first stimulate then inhibit the release of the pituitary hormones FSH and LH. Without gonadotropin stimulation, ovarian follicles do not develop and ovarian hormones including estrogen and progesterone, drop to low levels. These medications are commonly used to synchronize follicles and to reduce the likelihood of premature ovulation in ART cycles. The long acting depot form is used to treat endometriosis, fibroids, pelvic pain and prostate cancer.

### **Gonadotropin releasing hormone antagonist - GnRHant (Antagon, Cetrotide)**

GnRH antagonists are synthetic protein derivatives of the human hypothalamic hormone GnRH. They function by blocking the effect of naturally produced GnRH. The result is a rapid decrease in the pituitary hormones with resultant ovarian suppression which continues for as long as the medication is administered. These medications are given by subcutaneous injection.

### **SIDE EFFECTS**

Since the production of estrogen from the ovaries is reduced to post-menopausal levels, any post-menopausal symptom may occur. Most commonly noted are hot flashes but others include headache, insomnia, vaginal dryness and irritation, decreased libido, and lethargy. Injections can cause pain, swelling, itching, or irritation at the injection sites. Inhaled medications can cause nasal irritation. Numerous other side effects have been reported with low frequencies.

### **RISKS**

During the initial stimulation phase of GnRH agonist use, ovarian cyst formation may occur. Also, exacerbation of estrogen related medical problems such as endometriosis or fibroids might occur. These problems may require extension of the length of time for medication use or necessitate surgical treatment.

### **MISCARRIAGE, STILLBIRTH, AND FETAL CONGENITAL MALFORMATIONS (BIRTH DEFECTS)**

Both GnRH agonists and antagonists are rated pregnancy Category "X". This indicates that fetal risk has been clearly documented. There are over 100 pregnancies in women who inadvertently took GnRH agonists without ill effect. The numbers are too low to be meaningful. There is no indication in the medical literature that agonist or antagonist use increases the risk of fetal malformations when taken before pregnancy occurs.