

GONADOTROPINS: HOW THEY WORK AND THE RISKS AND SIDE EFFECTS ASSOCIATED WITH THEIR USE

Gonadotropins are hormones produced by the pituitary gland and which stimulate sex hormone production as well as gamete (sperm and egg) production in the man /woman. Hence the term “gonadotropins”. They are also responsible for the expression of secondary sexual characteristics such as hair growth, muscular development, and voice changes and breast development. There are two gonadotropins, Follicle stimulating Hormone (FSH) and Luteinizing hormone (LH). The gonadotropins are excreted in the urine. Two types are available pharmaceutically. The first, Human Menopausal Gonadotropins (hMG ;Repronex) is derived from the urine of menopausal women, and the second, Recombinant FSH (FSHr), is genetically engineered.

Human Menopausal Gonadotropins (hMG) –Repronex (Ferring): hMG is a good source of both FSH and LH. This is because a menopausal woman's pituitary gland, in response to a feedback message that her ovaries are no longer producing enough estrogen or inhibin, increases the output of FSH and LH in an effort to re-stimulate the failing ovaries. The excess FSH and LH is excreted in the urine. Urine used for hMG is distilled, filtered, and purified by an expensive process. One ampule of hMG (75 units) costs about \$60 in the United States, and the average woman might require 25 or more ampules per treatment cycle.

It has been postulated that the LH component of hMG directly stimulates the tissue surrounding the ovarian follicles (ovarian stroma), which propagates precursors that in turn produce male hormones (androgens). Some of these androgens may filter into the surrounding follicles and adversely affect egg development. It is also possible that some of the androgens could inhibit the proper development of the endometrial lining. In this way, ovarian androgen production induced by LH could have a deleterious effect on egg and embryo quality as well as on the potential for healthy implantation in the endometrium.

Recombinant FSH (Follistim-Organon & Gonal F- Serono): Human menopausal gonadotropin, has in recent times largely been supplanted by purified FSH, derived by way of genetic engineering that makes it possible to induce bacteria to produce the product. Known as Recombinant FSH (FSHr). This technology is widely used in the pharmaceutical arena. The active product is highly purified and per unit, appears to be more bioactive than urinary derived FSH products such as hMG. Instead of influencing the hypothalamus and pituitary gland to produce more hormones to stimulate follicular development (as is

the case with clomiphene), gonadotropins act directly on the ovaries and do not inhibit the function of estrogen or the enzymes of the cells lining the follicles. If administered in sufficient amounts beginning early enough in the menstrual cycle, gonadotropins will prompt the maturation of multiple follicles. The average number of eggs usually retrieved from a woman younger than 40 after gonadotropin stimulation-provided she has two ovaries-is usually between six and 15. On rare occasions, retrievals of more than 50 eggs have been reported.

Because gonadotropins cannot be absorbed through the stomach into the bloodstream, they must be administered by injection rather than in pill form. While hMg must be injected intramuscularly, FSHr can be administered subcutaneously, thereby rendering the injections easier to administer and far less painful. The usual injection schedule is from day 2 or 3 through day 8 to 12 of the menstrual cycle. During that time, patients are carefully monitored with a combination of blood tests and ultrasounds. Because multiple follicles mature, raising the risks of multiple pregnancies or ovarian hyperstimulation (excessive swelling of the ovaries), judicious use of these medications is warranted. In experienced hands, these medications are extremely safe and highly efficacious.

One of the most significant attributes of gonadotropins is the safety-valve effect on ovulation. No matter how well stimulated a woman becomes when she takes gonadotropins, she will be unlikely to ovulate until she receives an injection of the hormone, Human Chorionic Gonadotropin (hCG). Thus, if for any reason it is determined that the woman should not progress to ovulation, (e.g. the risk of multiple pregnancy or ovarian hyperstimulation is too high), the hCG is simply not administered. In that case, the ovaries will return to normal and no long term effects will occur.

Purified Urinary-Derived FSH (Bravelle –Ferring Pharmaceuticals)

This amounts to Repronex that has been processed further to extract almost all LH to the point that there is virtually no LH (<2%) remaining. It has equivalent efficacy to the Recombinant FSH (FSHr)

Risks and Side Effects of Gonadotropins

Many women taking gonadotropins report breast tenderness, backaches, headaches, insomnia, bloating, and increased vaginal discharge, which are directly due to increased mucus production by the cervix. This is the desired effect for patients being treated with gonadotropins for ovulation enhancement during intra-uterine inseminations (IUI).

Gonadotropins help to synchronize development of the endometrium with growth of the follicles and eggs. This synchronization is a critical prerequisite for successful implantation because IVF embryos are usually transferred to the uterus a few days earlier than they would reach it under natural circumstances. Therefore, accelerated endometrial development enhances the chances that the young embryos will implant after their transfer to the uterus.

Possible side effects of gonadotropin administration include over stimulation that can threaten the woman's well-being include enlargement and "weeping" of the ovaries, a condition in which a large amount of fluid is exuded into the abdominal cavity. In severe cases this can cause the abdomen to distend severely and may even compromise breathing. In rare cases the kidneys or liver may fail and the woman may stop producing urine, which can be life-threatening. In very severe cases her blood may lose

its ability to clot properly. These situations, however, are **extremely rare** and are sometimes caused by inappropriate use of gonadotropins, with inadequate monitoring of the patient while they are taking the medication. They are highly unlikely to occur in the properly managed cycle.

It is significant that gonadotropins are unlikely to produce any serious persistent side effects until the woman receives the injection of hCG to stimulate ovulation. Thus, the physician has ample time to assess her status and withhold the hCG if it appears that she might develop major side effects. (Such an assessment is made on the basis of blood estradiol values or ultrasound examinations immediately prior to administration of hCG.) This built-in protective advantage shields almost all women being treated with gonadotropins (administered either alone or in combination with clomiphene) from the serious hazards of over stimulation. In other words, in experienced hands, the use of these medications is quite safe.

Variations in Response to Gonadotropins:

Some women stimulate well after relatively small doses of gonadotropins. Others require two, three, or even four times that dosage to achieve the same effect. In the past, selecting the proper dosage was a trial-and-error process. There was simply no way to predict how a particular woman might respond. Each woman is unique, and each can be expected to react differently to gonadotropins. However, about 80% of women respond appropriately to an average injection. To a large extent, the first cycle of gonadotropin administration remains experimental for any particular patient and it is necessary to monitor more carefully in the first cycle, until the physician can get a clear understanding of how the patient is responding. Response in subsequent cycles is likely to be very similar (or weaker) than the response in the first cycle.

We measure FSH (follicle-stimulating hormone) and estradiol (E2) in the woman's blood on the second or third day of a natural menstrual cycle preceding the IVF cycle. We use the levels of these hormones to predict the probable way she will respond to a variety of stimulation methods. We believe these tests, along with BMI(body mass index, which is a function of height and weight), and underlying disease, patient age, are all valuable in selecting the most appropriate dosage and regimen of fertility drugs to be administered. In selected cases we can perform a “clomiphene challenge test “ which provides additional information as to how a woman might respond to a given dosage of gonadotropins.

Despite these refinements, however, stimulation for IVF is still somewhat of a hit-or-miss procedure. For example, when a woman has used up most of her lifetime egg budget and is left with less than a critical number of eggs, she begins to enter a phase of hormonal change known as the climacteric. The climacteric is associated with a loss of fertility, the onset of hot flashes, and mood changes. It ultimately culminates with the total cessation of menstruation between the ages of 40 to 55, a process called the menopause. The ovaries still produce hormones after menopause, but they are released in a constant rather than cyclical manner.

Ovarian Hyperstimulation Syndrome and “prolonged coasting”:

In certain circumstances despite careful monitoring, ovarian hyperstimulation might occur. It has been demonstrated that if more than 30 follicles develop following stimulation with fertility drugs and the woman's plasma estradiol at its highest level exceeds 6,000 picograms per milliliter, there could be as much as an 80% risk of ovarian hyperstimulation. Until recently, the only way to prevent these complications from occurring was by withholding hCG in those cases where over stimulation appeared to be taking place.

In cases where the development of severe hyperstimulation is suspected, so long as the follicles have reached a certain size (14mm), the gonadotropin therapy can be withheld. The estrogen levels can be carefully monitored and the hCG trigger will only be administered when it is safe enough to do so (Estrogen level of < 3000pg/ml). In this fashion, the cycle is saved and the patient is not exposed to the severe complications of ovarian hyperstimulation syndrome. There are cases where this is not clear cut and careful monitoring is needed to determine the optimal time of hCG administration. .

When a woman fails to become stimulated on the first try, hormone tests are indicated to ensure that she is not in the climacteric as well as to determine if hormonal abnormalities or other conditions might be inhibiting her sensitivity to gonadotropins. If she is not in the climacteric and no other abnormalities are detected, then it can be anticipated that she will eventually respond to an adjusted dosage of gonadotropins. She can begin another round of gonadotropin therapy with an adjusted dosage after she lets her body recover for a month or two. The reason for the delay is to allow receptor replenishment. {Receptors are proteins which bind gonadotropins to effectuate their intended action.}

Follicle growth and development, egg maturation, the number of eggs that can be retrieved, and the risk of side effects are directly related to the patient's response as evaluated by blood-estrogen levels and/or ultrasound, not necessarily to the dosage of gonadotropins. Therefore, it is illogical to fear administering an escalating dose of gonadotropins after a poor response to a standard dosage. What is important is to monitor the individual's response to the drug.

Combination of Clomiphene and Gonadotropins:

Occasionally, it may be prudent to administer a mixture of clomiphene and gonadotropins for controlled ovarian hyperstimulation. While the vast majority of IVF programs in the United States, no longer use this combination for IVF cycles, a significant number of pregnancies have been reported by the few programs that still use this method for IUI cycles. One of the reasons for using this combination is because clomiphene increases the ovaries' sensitivity to gonadotropins, thereby reducing the dosage of gonadotropins that must be administered.

Thus, the overall cost of the fertility drugs is significantly decreased by reducing the required amount of expensive gonadotropins. A second reason for administering these drugs in combination is to simplify their administration (clomiphene can be taken in pill form although gonadotropins must be injected).

Conclusion: Gonadotropins are the mainstay of treatment in Reproductive Medicine. It is true to say that without their use, no program would be able to function effectively and the millions of pregnancies that have been established worldwide, would not have come to fruition. Like anything, there are risks associated with their use. Mainly, these include multiple pregnancies and ovarian hyperstimulation. Minor risks, such as pain or redness at the injection site, are also a factor. In experienced hands,

gonadotropins are highly efficacious and safe. In particular, since the advent of coasting, the risks of severe ovarian hyperstimulation syndrome have all but been completely eliminated. The cost of the medication and the fact that they need to be administered by injection rather than by mouth, remain the major drawbacks. However, when all things are considered, the advantages far outweigh the disadvantages attendant in their use.

Rev. 10/07

This handout is intended as an aid to provide patients with general information. As science is rapidly evolving, some new information may not be presented here. It is not intended to replace or define evaluation and treatment by a physician.