



PATIENT'S FACT SHEET

Side Effects of Gonadotropins

Gonadotropins are fertility medications given by injection. They contain follicle-stimulating hormone (FSH), which is produced naturally by the pituitary gland, alone or combined with luteinizing hormone (LH), also produced by the pituitary gland. A related medication is human chorionic gonadotropin (hCG) which is structurally similar to LH and which simulates the natural LH surge that causes ovulation at midcycle.

Gonadotropins are used to induce follicular development and ovulation in women who do not ovulate. They also are used to induce development and ovulation of multiple follicles in women undergoing advanced reproductive therapies such as in vitro fertilization or superovulation and intrauterine insemination. HCG is commonly used to trigger ovulation once follicles have developed to maturity. There are a variety of gonadotropins commercially available and others in various stages of research and development. Careful monitoring of patients is required when gonadotropins are used in order to minimize the risk of side effects:

1. Ovarian Hyperstimulation Syndrome (OHSS). OHSS is characterized by enlarged ovaries and fluid accumulation in the abdomen after ovulation or egg retrieval. It can be either mild or severe. The mild form occurs in 10% to 20% of cycles and results in some discomfort but almost always resolves without complications. The severe form occurs approximately 1% of the time. The chance of OHSS is increased in women with polycystic ovarian syndrome and in cycles resulting in pregnancy. When severe, it can result in blood clots, kidney dysfunction, twisting of an ovary (torsion), fluid collections in the chest and abdomen, and rarely even death. In severe cases, hospitalization is required for monitoring but the condition is transient, usually lasting only a week or two. Occasionally, draining the excess fluid is needed to decrease symptoms. Most patients who are at high risk for severe OHSS are identified by closely monitoring ovulation induction cycles with the daily use of ultrasounds and/or serum estradiol levels. When serum estradiol levels are rising rapidly and/or are too high, or excessive numbers of ovarian follicles develop, one strategy for prevention of severe OHSS 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. In some IVF cycles in which OHSS is felt to be a high likelihood, a recommendation may be made to administer hCG, retrieve oocytes, but cryopreserve all embryos for use in future cycles.

2. Multiple Gestation. Up to 30% of pregnancies which result from cycles involving gonadotropin stimulation are multiple, in contrast to a rate of 1% to 2% without fertility medications. The risk of multiple gestation is dependent upon the number of mature eggs released in an ovulation induction cycle and the number of embryos transferred in an IVF cycle. While most of these pregnancies are twins, a significant percentage (up to 5%) are triplets or higher. Compared to singletons, twins and high order (more than two) multiple gestation pregnancy are associated with an increased risk of pregnancy loss, premature delivery, infant abnormalities, handicap due to the consequences of very premature delivery, pregnancy induced hypertension, hemorrhage, and other significant maternal complications. In general, the risk of severe complications increases as the number of gestations increases. There is a suggestion in some studies that the number of low birth weight in infants may be increased in even singleton pregnancies.

3. Ectopic (Tubal) Pregnancies. While ectopic pregnancies occur in 1% to 2% of spontaneous pregnancies in the general population, in gonadotropin cycles the rate is slightly increased. Ectopic pregnancies can be treated with medications or surgery. Occasionally a tubal pregnancy occurs at the same time as an intrauterine pregnancy; this condition is known as heterotopic pregnancy and may be difficult to diagnose.

4. Adnexal Torsion (Ovarian Twisting). In less than 1% of gonadotropin cycles the stimulated ovary can twist on itself, cutting off its own blood supply. Surgery is required to untwist or remove the ovary.

5. Gonadotropins and Ovarian Cancer. Although early studies suggested that the risk of ovarian cancer might be increased in women exposed to medications for ovulation induction, more recent studies have not shown any such relationship. It is generally felt that gonadotropin therapy does not increase the risk of ovarian cancer.

6. Adverse Pregnancy Outcomes. Although the vast majority of pregnancies are entirely normal, recent studies suggest the possibility that complications during pregnancy may be increased slightly. Pregnancy-associated hypertension and abruption of the placenta may be increased. It is not clear if the risks are related to the gonadotropin therapy or are related to the infertility.

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FSH (Follistim, Gonal-f, Bravelle)

FSH/LH Combination (Repronex, Menopur)

The FSH medication is genetically engineered (recombinant) forms of FSH (Follicle Stimulating Hormone) which are used to stimulate the recruitment and development of multiple eggs in women during an ovulation induction cycle.

Due to the variability in response from patient to patient, no fixed dosage regimen can be recommended. Each patient cycle must be individualized. This will require ultrasound exams and blood estrogen levels to assess ovarian response.

FSH is available only in an injectable form. You will need to learn injection techniques. FSH is administered by subcutaneous (SQ) injection techniques. This injection should be given between 6 and 9 pm each evening.

Side effects may include: ovarian enlargement, hyperstimulation syndrome, multiple gestation, abdominal pain, and headache. Discomfort and bruising may occur at the injection site. Monitoring with ultrasounds and estradiol minimizes the risk of complications.

hCG (Ovidrel) Human Chorionic Gonadotropin

HCG is a natural hormone that helps with the final maturation of the eggs and triggers the ovaries to release the mature eggs (ovulation). It also stimulates the corpus luteum to secrete progesterone to prepare the lining of the uterus for implantation of the fertilized egg. Ovulation (follicle rupture) usually occurs about 38-40 hours after the hCG is given. hCG is available in an injectable form.

Side effects may include: headaches, irritability, restlessness, depression, fatigue, edema, and ovarian hyperstimulation.

Leuprolide (Lupron) Synthetic Gonadotropin (FSH/LH) Inhibitor

Lupron suppresses the brain's secretion of LH and FSH; therefore, it is used in preparation for cycles of treatment with ovulation induction drugs (FSH). It improves the recruitment of follicles by preventing the recruitment of a dominant follicle for the next menstrual cycle. Lupron enables the ovaries to respond with the recruitment of multiple follicles since in most cases we are able to override the selection of a single dominant follicle. It will also prevent premature ovulation (release of eggs) by preventing LH release.

To confirm the effectiveness of the Lupron treatment, an ultrasound will be performed before the ovarian stimulation is initiated.

Lupron is available in an injectable form. Therefore, you will be instructed on subcutaneous (SQ) injection technique. The multidose vial should be kept cool (< 75°F) - refrigeration is OK. This drug should be given at the same time everyday (1 hour leeway). If you are starting Lupron after a spontaneous menstrual cycle (no oral contraceptive pills) you should use barrier contraception for the preparatory cycle.

Side effects may include: hot flashes, vaginal dryness, and skin rash. Side effects of long-term treatment (greater than six weeks) include hot flashes, vaginal dryness, and bone loss. These side effects are extremely rare after short-term use associated with standard IVF. No long-term side effects after treatment occur.

Facts about Ovarian Hyperstimulation Syndrome (OHSS)

The medications used to stimulate your ovaries may cause side effects. These side effects can range from mild to severe. Excessive stimulation of the ovaries is called ovarian hyperstimulation. This may require removing some of the fluid in our office and/or a hospital stay in approximately 1 % of the patients. Be aware of body changes and ask your primary nurse if you have any questions or concerns. She will contact the physician if necessary. You may have symptoms of mild hyperstimulation during your treatment cycle, however, moderate and severe symptoms usually occur 6-8 days after treatment ends.

SIGNS AND SYMPTOMS	WHY IT HAPPENS	WHAT TO DO
Mild You may experience: - Abdominal bloating and feeling of fullness - Nausea - Diarrhea - Slight weight gain	This may be due to: - Ovaries are larger than normal, tender and fragile - High level so estrogen (E2) and progesterone in the bloodstream may upset your digestive system and fluid balance causing bloating.	Recommended treatment: - Avoid sexual intercourse - Do not have a vaginal (pelvic) exam other than by one of our physicians - Reduce activities, no heavy lifting, straining or exercise - Drink clear fluids, flat coke, ginger ale, cranberry juice, Gatorade or Ensure
Moderate You may also experience: - Weight gain of greater than 2 lbs. per day (excessive weight gain) - Increased abdominal measurement causing clothes to feel tight - Vomiting & diarrhea - Urine is darker and amount is less - Skin/hair may feel dry - Thirst	This may be due to: - High levels of hormones in the bloodstream upset the digestive system - Fluid imbalance causes dehydration because body fluids collect in the abdomen and other tissues - This fluid collection causes severe bloating	As noted above plus: - Call our nurses - You may need to be seen by a physician who will do an ultrasound - Record your weight twice daily - Record the number of times you urinate each day - Contact our office if you note a five pound weight gain over the previous 24 hours, note a drop in the frequency of urination (~50%), or increasing pelvic pain
Severe You may also experience: - Fullness/bloating up above the belly button - Shortness of breath - Urination has reduced or stopped and become darker - Calf pains and chest pains - Marked abdominal bloating or distention - Lower abdominal pain	This may be due to: - Extremely large ovaries - Fluid collects in lungs and/or abdominal cavity, as well as in tissues - The risk of abnormal blood clotting increases	As noted above plus: - Notify the physician on call - You may need to be assessed at the hospital or our clinic - Excess fluid may need to be removed from your abdominal cavity

If your period starts, you will likely begin to feel better. Pregnancy may prolong or exaggerate these side effects. It may take up to 10 weeks for the symptoms to resolve if you are pregnant.