Ovarian Stimulation Protocols for IVF

The goal of ovarian stimulation during an IVF treatment is to harvest 8-15 good quality eggs. There are several ovarian stimulation medication protocols that are used to accomplish this goal. All of the commonly used ovarian stimulation protocols generally involve the patients taking 3 types of drugs: 1

- A medication to suppress LH surge and ovulation during ovarian stimulation with gonadotropins. The two classes of drugs used to inhibit LH surge during IVF treatment include:  
  - GnRH (Gonadotropin Releasing Hormone) agonist – Lupron
  - GnRH antagonist – Ganirelix Acetate or Cetrotide

- Gonadotropins - injectable hormones used to stimulate follicular growth on the ovary. Women are usually on these drugs for 8-12 days until multiple mature follicles have developed.
  - Follistim – recombinant FSH
  - Gonal-f - recombinant FSH
  - Bravelle – urinary FSH
  - Menopur – purified HMG (FSH + LH) derived from urine
  - Repronex - HMG (FSH +LH) derived from urine
  - Luveris – recombinant LH

3. HCG (Human Chorionic Gonadotropin) to cause final maturation of the eggs.

Based on a patient’s treatment prognosis, an infertility specialist will choose the best ovarian stimulation medication protocol and dosing regimen. Follicular growth and blood levels are monitored closely throughout ovarian stimulation to allow the physicians to adjust doses where needed. Peak estrogen levels in IVF at the time of HCG are usually between 1000-4000 pg/ml. When lead follicles reach approximately 18-20 mm in diameter, physicians will direct patients to take HCG to final maturate the eggs.

Egg retrieval is typically scheduled 34-35 hours after the HCG injection has been given.

The most commonly used protocols for IVF are:

- Luteal Lupron protocol – also called “long Lupron”, or agonist “down regulation”
- Antagonist protocol – that involves the use of GnRH antagonist medications
- Flare and micro-flare protocols – also called “short Lupron” protocols – these protocols are for patients expected to have a low response to ovarian stimulation

- Stop Lupron protocol – given when patients are expected to “over-suppress” on the standard “long Lupron protocol”

**Luteal Lupron or Agonist Down Regulation Protocol**

The most widely used protocol in IVF is the Agonist “down regulation” protocol. Most specialists believe this protocol yields the best success rates for most patients. In this protocol leuprolide (10 units) is started about 7 days (cycle day 21 of a 28 day cycle) before the next expected period. Gonadotropins are usually started on the 2\textsuperscript{nd} or 3\textsuperscript{rd} day after the period begins. (Cycle day 2 or 3) The leuprolide dose is usually cut in half (5 units) at the time gonadotropins are started and continued until the day of HCG. Gonadotropin doses can range from 150-450IU per day and are commonly adjusted throughout the stimulation cycle based on ovarian response.

See example calendar of a Luteal Lupron calendar below:

<table>
<thead>
<tr>
<th>Sunday</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Start Lupron</td>
<td>Lupron</td>
<td>Menstrual cycle day 22</td>
<td>2</td>
<td>Menstrual cycle day 22</td>
<td>3</td>
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</tr>
<tr>
<td>8</td>
<td>Lupron</td>
<td>Lupron</td>
<td>FSH</td>
<td>9</td>
<td>Lupron</td>
<td>10</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Blood and ultrasound</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Day 1 of stimulation</td>
<td></td>
<td>Day 2 of stimulation</td>
<td>Day 3 of stimulation</td>
</tr>
<tr>
<td>15</td>
<td>Lupron</td>
<td>FSH</td>
<td>Blood and ultrasound</td>
<td>16</td>
<td>Lueprion</td>
<td>17</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>HCG injection</td>
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<td></td>
<td></td>
<td></td>
<td>Day 7 of stimulation</td>
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<td>Day 8 of stimulation</td>
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Stop Lupron Protocol

Some women might not stimulate well on the standard Luteal Lupron protocol due to “over-suppression” or might just be a poor responder for other reasons. In this situation, a physician may decide to implement the stop Lupron protocol in a subsequent attempt. The Stop Lupron protocol has the patient starting Leuprolide at the same time as the Luteal Lupron protocol but the dose is usually reduced by half (5 units). The leuprolide is then stopped completely after the woman gets her period and the gonadotropins are started. ¹

The LH suppressing ability of the Stop Lupron protocol is not as complete as the standard luteal Lupron protocol but the risk of spontaneous LH surge is low.

Often times when ovulation is more likely to happen during ovarian stimulation protocols, physicians may choose to watch more closely progesterone blood levels. Assuring that progesterone levels aren’t rising during gonadotropin treatment, physicians are informed that ovulation has not occurred or is about to. If the progesterone level is above 3.0 ng/ml, this usually indicates that ovulation has already taken place. Finally, LH or leutenizing hormone, may also be measured, as a sudden rise may indicate that ovulation is about to happen.

Micro-Flare and Flare Protocols

Women expected to have a poor ovarian response due to low antral follicle counts, age, or elevated FSH levels may be put on a microdose flare protocol. In this protocol, birth control pills are given for the month before to avoid the reactivation of a cyst (corpus luteum) by high LH levels at the onset of the flare stimulation. After the OC’s have been discontinued, no meds are given for two days. On the third pill free day, the woman begins taking micro-doses of Lupron (40-50 micrograms) twice daily. This leuprolide dilution must be done by either the pharmacy or the doctor’s office. This is a very low Lupron dose compared to the Lupron (.5 mg or 500 micrograms) dose administered in the Luteal Lupron protocol described above. On the day after the first micro-dose leuprolide injection, gonadotropin injections are started. Micro-dose injections of Leuprolide are usually continued until the day of HCG. ¹
It’s important to remember that this protocol is trying to help poor responders by letting them take advantage of the FSH & LH flare that occurs in the initial days of taking Leuprolide. If you would like further clarification about the flare up of FSH & LH that occurs in the beginning stages of taking leuprolide, please review the mechanism of action of leuprolide in module 3.

If the micro-dose flare protocol doesn’t work well, it may be determined that this subset of patients (poor responders) can’t get pregnant using their own eggs. At this point IVF with donor eggs may be considered.

**Antagonist Protocols**

Antagonist protocols use GnRH antagonist such as Ganirelix Acetate or Cetrorelix Acetate to inhibit LH surge during ovarian stimulation cycles. The antagonist came to market in 2000 and since then they have been widely used with great success in many different types of patients. Patients on an antagonist protocol usually start gondotropins on the 2nd or 3rd day menses and begin taking the antagonist on FSH treatment day 6 or cycle day 8. Patients will remain on the antagonist until the day of HCG. The obvious advantage of this protocol over the agonist protocols is that patients will take significantly less shots.  

**High Responder Protocols**

Often times women diagnosed with PCOS will be a hypersensitive to gonadotropin therapy. Stimulating PCOS patients remains a controversial topic among infertility specialist and the optimal stimulation protocol is still under debate. Currently the most standard protocol is the “agonist down regulation” protocol associated with FSH. PCOS patients are usually started on lower gonadotropins doses in effort to control excessive follicular development.  

It has been suggested that increased luteinizing hormone (LH) secretion in PCOS patients may interfere with fertility. Excessive LH in PCOS patients may cause oocytes to mature prematurely and effect hormone production at a granulose cell level. In addition it has also been suggested that elevated LH levels may lead to increased pregnancy loss, although recent data are not consistent with this assumption.  

PCOS patients are prone to excessive follicular development during ovarian stimulation therefore patients are monitored more intensely to reduce the chances of OHSS. Experts agree that IVF treatment with single embryo transfer vs. ovulation induction markedly reduces the risk of multiple pregnancies for PCOS patients.  

Experts also agree that more research is needed comparing FSH stimulation protocols with use of GnRH agonist versus GnRH antagonist.  