

## **The Need for an Individualized Approach to COH**

***Preparing for COH with Gonadotropins:*** It is advisable that one or two months be allowed to elapse (the “resting cycle”) between IVF treatment cycles, in order to allow the ovaries to fully recover. It is also important to ensure that the plasma estradiol (E2) level is below 70 picograms per milliliter following successful pituitary LH suppression (with GnRH agonist or antagonist), prior to initiating COH. The best time to measure the E2 level is soon after (i.e., within days) the onset of Lupron-induced menstruation. The most common cause of an elevated blood E2 level around this time is the existence of one or more ovarian follicular cysts. These should be allowed to heal on their own or be aspirated prior to proceeding. Spontaneous absorption will usually occur with continued LH suppression using agonist/antagonist. If this fails to occur, the cyst should be aspirated under local anesthesia, prior to initiating COH. The use of an oral contraceptive will reduce the likelihood that an ovarian cyst will occur.

***Selecting the ideal protocol for COH:*** In order to maximize the quality and number of oocytes a woman produces, the oocytes must be able to complete their growth and development. A fruit plucked from a tree prematurely might still ripen (mature) on the shelf and might even appear as enticing as one that had previously undergone proper development, but it will lack the same quality. The same principle applies to the development and maturation of human eggs. Proper developmental stimulation as well as precise timing in the initiation of LH or hCG are crucial to the success of the cycle. In cases where egg maturation is improperly timed, there is an increased risk of aneuploidy (structural and numerical chromosomal abnormalities) leading to a failure to become pregnant or a pregnancy destined to miscarry. The potential for eggs to undergo orderly maturation, successful fertilization and subsequent development into “good quality embryos” is in large part, genetically determined. However, the expression of this potential is profoundly susceptible to numerous extrinsic influences, especially intra-ovarian hormonal changes during the pre-ovulatory phase of the cycle.

During the normal ovulation cycle, ovarian hormonal changes are regulated to avoid imbalance that could adversely influence follicle development and egg quality. As an example, while small amounts of ovarian male hormones (androgens) such as testosterone enhance egg and follicle development, over-exposure to the same hormones can compromise egg quality enough to prevent fertilization or simply ensure an adverse outcome. That’s why a woman’s protocol for controlled ovarian hyperstimulation (COH) should be geared toward optimizing her follicle development and her exposure to androgens. To achieve this requires an individualized approach to COH and precise timing of the ovulatory “trigger.”

It is important to recognize that the pituitary gonadotropins FSH and LH, while both playing a pivotal role in follicle development, induce very different actions within the ovary. The function of FSH is mainly directed toward promoting the proliferation of granulosa cells—the helper cells which line the inside of the follicles so they can produce estradiol and the other hormones necessary to support egg maturation. LH, on the other hand, acts primarily on the thecal cells within the ovary’s connective tissue to promote the production of testosterone. Only a small amount of testosterone is necessary to serve as the precursor for optimal estrogen production. Over-production has a deleterious effect on granulosa cell activity, follicle growth/development, egg maturation, fertilization potential and subsequent embryo quality. Furthermore, excessive ovarian androgens can also compromise estrogen-induced endometrial growth and development.

In conditions such as polycystic ovarian syndrome (PCOS), which is characterized by increased blood LH levels or LH activity, there is also an increased ovarian androgen production. It is therefore not surprising that “poor egg/embryo quality” and inadequate endometrial development are often features of this condition. The use of LH-containing preparations such as Menopur and Repronex further aggravates this effect. Thus we strongly recommend against the exclusive use of such products in PCOS patients, preferring FSH-dominant products such as Bravelle and Gonal-F. While it would seem prudent to limit LH exposure in all cases of COH, this appears to be more relevant in older women, who tend to be more sensitive to LH activity.

It is common practice of many fertility centers to administer gonadotropin releasing hormone (GnRH) agonists (e.g. Lupron, Buserelin) and more recently, GnRH-antagonists (e.g. Ganirelix, Cetorelix, Cetrotide ) to prevent the spontaneous release of LH during COH. GnRH agonists however, only exert their LH-lowering effect after a number of days. They do so by causing an initial outpouring and then a depletion of FSH and LH from the pituitary. As a result, LH levels should fall to a negligible amount within 4-7 days, thereby establishing a relatively “LH-free environment.” GnRH antagonists, on the other hand, act rapidly – within a few hours – to block pituitary LH release and produce the same effect. Here are the various ways these medications are actually used:

### **Long GnRHa Protocols**

Here the GnRHa (usually Lupron) is given for a few days before the stimulation with gonadotropins and begins to induce an FSH surge. The purpose of this surge is to “recruit follicles” for the stimulation with gonadotropins that follows the agonist-induced menstrual bleed. This mimics what occurs in a natural cycle. There are three options that are commonly used:

- 1. GnRHa Throughout:*** The most commonly prescribed protocol for long GnRHa /gonadotropin administration involves starting the GnRHa for 5-7 days prior to menstruation. This precipitates an initial rise, and then a drop in FSH and LH levels,

resulting in uterine withdrawal bleeding (menstruation). Thereupon, gonadotropin treatment is initiated while daily GnRHa injections continue, to ensure a relatively low-LH ovarian environment.

**2. Agonist/Antagonist Conversion Protocols (A/ACP):** About 5 years ago, we developed a variation on the Long GnRHa protocol. With the A/ACP, as soon as menstruation starts, we supplant the agonist with a low dose antagonist. With a few notable exceptions at SIRM, we often prescribe the A/ACP rather than the traditional “GnRHa Throughout” long protocol. We almost always prescribe 125mg Ganirelix or Cetrotide (i.e. half the usual dosage) starting on the day that FSH-dominant gonadotropin (Follistim or Gonal-F) stimulation is initiated. The intent is to purposefully allow only a small amount of the woman’s own pituitary LH to enter her blood while preventing a large amount of LH from reaching her circulation. The end result is an optimal hormone balance for healthy egg development.

**3. A/ACP with Estrogen priming:** Women who have demonstrated a prior reduced ovarian response to COH as well as those with tests suggesting reduced ovarian reserve are considered likely to be “poor responders.” In these cases, patients are first given GnRH agonist for a number of days to achieve pituitary down-regulation. Upon menstruation and confirmation by ultrasound blood estradiol measurement that adequate ovarian suppression has been achieved, the dosage of GnRH agonist is drastically lowered (or the agonist is replaced with a GnRH Antagonist) and the woman is given twice-weekly injections of estradiol for a period of 7-10 days. COH is then initiated using a relatively high dosage of FSH-only gonadotropins such as Follistim or Gonal-F. The FSH stimulation is continued along with daily administration of GnRH agonist/antagonist until the “hCG trigger.” A recently completed study demonstrated the efficacy of this protocol and the ability to significantly improve ovarian response to gonadotropins in many previously “resistant” patients.

### **Short GnRHa (“Microflare”) Protocols**

Another approach to COH is by way of so-called “microflare protocols.” This involves initiating gonadotropin therapy simultaneous with the administration of GnRH agonist. The intent is to deliberately allow GnRHa to effect an initial surge (“flare”) in pituitary FSH release so as to augment ovarian response to the gonadotropin medication. Unfortunately, this approach represents “a double-edged sword” as the resulting increased release of FSH is likely to be accompanied by a similar rise in blood LH levels that could evoke excessive ovarian stromal androgen production. The latter could potentially compromise egg quality, especially in women with diminished ovarian reserve (often older women) and in women whose ovaries have increased sensitivity to LH like those with polycystic ovarian syndrome

(PCOS). We believe that in this way, “microflare protocols” could potentially have a negative impact upon endometrial development, compromise egg/embryo quality, and reduce IVF success rates. Accordingly, we prefer to avoid “flare protocols”.

### **Mid-Follicular Antagonist Protocols**

The standard use of GnRH antagonists (i.e. the administration of 250mcg daily from the 6th or 7th day of stimulation) with gonadotropins may be problematic, especially in women over 40 years of age, “poor responders” to gonadotropins, and women with PCOS. In such cases, the initiation of pituitary suppression with GnRH antagonists so late in the cycle of stimulation fails to suppress high tonic pituitary LH in the most formative (early) stage of folliculogenesis.

Presumably, the reason for the suggested mid-follicular initiation of high dose GnRH antagonist is to prevent the occurrence of the so called “premature LH surge”, which is known to be associated with “follicular exhaustion” and poor egg/embryo quality. However the term “premature LH surge” is a misnomer and the concept of this being a “terminal event” or an isolated insult is erroneous. In fact, the event results from a culmination of the progressive escalation in LH (“a staircase effect”) which results in increasing ovarian activation with progressively growing androgen production. Trying to improve ovarian response and protect follicular exhaustion by administering Ganirelix/Cetrotide during the final few days of ovarian stimulation is like trying to prevent a shipwreck by removing the tip of an iceberg to prevent a collision.

The use of such mid-follicular Ganirelix/Cetrotide protocols in younger women or in normal responders will probably not produce such adverse effects because the tonic endogenous LH levels are low (normal) in such cases and such normally ovulating women rarely have hyperplasia of ovarian cells that produce testosterone. However, such women would probably not require any pituitary suppression or down-regulation anyway.