Luteolysis induced by a gonadotropin-releasing hormone agonist is the key to prevention of ovarian hyperstimulation syndrome

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**Objective:** To review the available knowledge on the use of GnRH agonist for ovulation triggering as a means to prevent ovarian hyperstimulation syndrome (OHSS).

**Design(s):** Review of pertinent English language studies published over the past 15 years.

**Result(s):** The available literature suggests that while GnRH agonist effectively induces final oocyte maturation and ovulation, it also completely and reliably prevents clinically significant OHSS. The mechanism of action in the context of OHSS prevention involves complete, quick, and irreversible luteolysis.

**Conclusion(s):** Controlled ovarian stimulation protocols based on GnRH antagonist to prevent premature LH rise and GnRH agonist for ovulation triggering provide a safe and OHSS-free clinical environment. Adequate luteal support compensates for luteolysis and assures good clinical outcome. The fertility community is urged to adopt these protocols. This will make OHSS a disease of the past. (Fertil Steril® 2004;81:1–5. ©2004 by American Society for Reproductive Medicine.)

**Key Words:** OHSS, prevention, GnRH agonist, GnRH antagonist, luteolysis, ovarian stimulation, ovulation

Human menopausal gonadotropin (hMG) has been used for decades in ovulation induction cycles, particularly in the context of IVF. In recent years, recombinant FSH preparations have replaced hMG in most centers. Typically, in these cycles, hCG is used as a surrogate for LH for the purpose of oocyte maturation and induction and ovulation. Given its significantly longer half-life (>24 hours (1, 2)), hCG administration results in a prolonged lutetrophic effect, which is characterized by the development of multiple corpora lutea and supraphysiologic levels of E₂ and P. This sustained lutetrophic effect may result in the development of ovarian hyperstimulation syndrome (OHSS), the most frequent and severe complication of ovarian stimulation treatments (3).

A World Health Organization report states that the worldwide incidence of severe OHSS is 0.2%–1% of all assisted reproductive technology (ART) cycles, with a 1:45,000–1:50,000 mortality rate per infertile women receiving gonadotropins. After IVF, the overall incidence is estimated to be 0.6%–14% (4). These numbers translate to >10 deaths and thousands of hospitalizations annually worldwide.

An alternative to hCG-driven ovulation is the use of gonadotropin-releasing hormone agonists (GnRHa). These compounds induce a sustained release of LH (and FSH) from the pituitary (also known as the “flare effect”) that effectively induces oocyte maturation and ovulation. Importantly, they also provide a means by which OHSS is completely and effectively eliminated (5–12). The use of this approach was limited until recently, given its inapplicability in GnRHa-induced pituitary down-regulation–based protocols. The introduction of GnRH antagonists in ovarian stimulation protocols has renewed the interest in using GnRHa to trigger ovulation, while eliminating any threat of clinically significant OHSS.

**The Spontaneous LH/FSH Surge**

The midcycle spontaneous LH surge is characterized by three phases: a rapidly ascending limb 14 hours in duration, a plateau of 14 hours, and a descending phase of 20 hours (13). The parallel FSH surge is of lower am-
plitude. Serum E₂ levels reach a peak at the time of the onset of LH surge and then decline rapidly. Serum levels of P begin to rise 12 hours before LH surge, continue to rise for an additional 12 hours, and then plateau until follicular rupture (36 hours after LH surge onset). Follicular rupture is associated with a second rise in P and a fall in E₂ as the luteal pattern of ovarian steroidogenesis is attained.

The threshold duration of LH surge required for the final stage of follicular and oocyte maturation has been studied in primates. Based on these studies (14, 15), 14–18 hours of LH surge are required to reinitiate oocyte meiosis, while metaphase II oocytes are obtained after a 28-hour exposure to LH.

**The GnRHa-Induced LH/FSH Surge**

GnRHa elicits pituitary secretion of gonadotropins, which can be used for triggering oocyte maturation and ovulation if given at the right time of the cycle. Numerous compounds, administered in different regimens, have been successfully used for that purpose (3–12). Based on these studies, it appears that a single administration of a GnRHa in a dose of 200–500 μg effectively and reliably triggers the required gonadotropin surge (11, 12). However, the minimal effective dose of GnRHa required to trigger an endogenous midcycle LH surge sufficient to induce oocyte maturation and ovulation remains to be established. Preliminary experience (16) suggests that a single dose of 50 μg of intranasal buserelin is the minimal effective dose to trigger ovulation.

The pituitary and ovarian responses to midcycle GnRHa injections in stimulated cycles were described elsewhere (8). The injection of GnRHa results in an acute release of LH and FSH. The serum LH and FSH levels rise during 4 and 12 hours, respectively, and are elevated for 24–36 hours. The amplitude of the surge is similar to that seen in the normal menstrual cycle, but by contrast with the natural cycle, the surge consists of only two phases: a short ascending limb (>4 hours) and a long descending limb (>20 hours). This has no bearing on the ovarian hormone secretion pattern, which is qualitatively similar to the pattern observed in a natural cycle. The LH surge is associated with a rapid rise of P and the attainment of peak E₂ levels during the first 12 hours after GnRHa administration. This is followed by a transient suppression of P biosynthesis and a gradual decline in E₂ levels during the 24 hours preceding follicle aspiration. After oocyte retrieval, a second rapid rise in P and continuous fall in E₂ are observed, which reflect normal early transition from follicular to luteal phase in ovarian steroidogenesis.

**The Luteal Phase**

While the endogenous LH surge triggered by GnRHa is associated with a normal follicular-luteal shift in ovarian steroidogenesis, serum levels of E₂ and P during the luteal phase are lower compared with those achieved after hCG administration (8). This may be related to the longer duration of plasma hCG activity compared with the shorter GnRHa-induced LH elevation. Normal function of the corpus luteum is dependent on pituitary LH (17). It is possible, therefore, that the partial down-regulation of pituitary GnRH receptors after a midcycle injection of a GnRHa results in reduced LH support for the developing corpora lutea, reduced steroidogenesis, and early luteolysis.

Indeed, recent evidence supports the notion that a midcycle injection of a GnRHa generates a dramatic luteolytic process. In a randomized multicenter study, Fauser et al. (18) compared the efficacies of two different GnRH agonists with that of hCG for triggering the final stages of oocyte maturation after ovarian hyperstimulation for IVF. They found that the final stages of oocyte maturation can be induced effectively by a single bolus injection of GnRH agonist, as demonstrated by the induced endogenous LH and FSH surges and the quality and fertilization rate of recovered oocytes. All patients received supplementation with exogenous P; therefore, E₂ levels can be taken to reflect endogenous luteal activity. As early as the day of ET, E₂ levels in the two agonist groups were about one-third the levels in the hCG group. In the midluteal phase, E₂ levels in the agonist groups were 46 and 45 pg/mL (vs. 490 pg/mL in the hCG group).

These very low levels reflect dramatic luteolysis induced by the agonists. In fact, these levels are even lower than those achieved in a natural cycle. The above conclusion is further supported by assessment of nonsteroidal markers of luteal activity, namely, inhibin A and pro-αC. In a similar study design (19), it was shown that midluteal levels of these peptides in the agonist groups were not only 18–40 times lower than those in the hCG group, they were also significantly lower than the levels found in a natural cycle (20). Of note, patients in the agonist groups who became pregnant did not show any recovery of inhibin A and pro-αC levels. Apparently, the endogenous, pregnancy-associated hCG, could not “revive” the corpora lutea.

Taken together, these findings clearly demonstrate dramatic luteolysis; therefore, it is necessary to support the luteal phase with P (and possibly E₂) in patients treated with midcycle GnRHa. Continued support during early pregnancy (until the luteal-placental shift) is probably required. We routinely initiate luteal support (micronized P 600 mg and E₂ 4 mg daily, both given vaginally) on the day of oocyte retrieval.

**Prevention of OHSS**

The most important benefit emerging from the use of GnRHa, rather than hCG, for ovulation induction is the ability of this regimen to completely eliminate the threat of clinically significant OHSS. It should be emphasized that the clinical findings attributable to mild (21) OHSS (e.g., ovarian enlargement, abdominal discomfort, and excessive steroid production) are an integral part of most cases of ovula-
tion induction in IVF and hence are meaningless in this context. As mentioned above, the clinical experience with midcycle administration of GnRHa in the context of OHSS prevention is very encouraging. Effective ovulation is triggered with no risk of OHSS even in patients with extremely high E2 levels during the late follicular phase (10).

Previous reports described cases in which OHSS developed despite the use of GnRHa to induce ovulation. Three cases were reported by van der Meer et al. (22). The clinical details of these cases are in line with mild to moderate OHSS. Severe ascites, hypovolemia, or electrolyte imbalance did not occur, nor were the patients hospitalized. Of note, the three patients received nasal GnRHa preparations (buserelin; Superfact; Hoechst, Germany). In one of them, a very weak response to GnRHa was noted, with an LH surge peak of 15.9 mIU/mL, which suggests that the dosage used or the route of administration were less than optimal. Clearly, the possibility of incomplete absorption using nasal administration cannot be ignored. In addition, the three patients were stimulated in preparation for intrauterine insemination (IUI).

Gerris et al. (23) have also reported OHSS following this approach; however, in this case, native GnRH (and not GnRHa) was used, which resulted in successful ovulation triggering, but without the critical gonadotropin suppression and luteolysis, which is the key element in preventing OHSS. Shoham et al. (24) reported a personal communication in which two cases of OHSS were described; however, the complete details of the treatment protocols, symptoms, and signs leading to the diagnosis of OHSS, severity of the syndrome, and clinical outcome were not available.

Lastly, a group from Saudi Arabia has presented its large and impressive experience with this strategy (25). Of 708 high-responder IVF patients with polycystic ovaries (mean E2 on the day of ovulation triggering = 7,817 pg/ml!), ovulation was effectively triggered with GnRHa in 682 (96%). One patient (0.1%) developed severe OHSS. Significantly, this patient was treated with hCG-based luteal support, probably by mistake, as the protocol dictated P-only luteal support. Also of note is that in 26 patients, the GnRHa-induced LH surge was judged as “inadequate.” In 18 of these patients, hCG was used, resulting in 11 (61%) cases of severe OHSS. This last figure may reflect the large number of severe OHSS cases in this series that were prevented by this strategy.

The reason(s) for inadequate LH surge may have to do with the dose (too low) or route (intranasal) of the GnRHa. A key point in this strategy is the ability of an adequate single dose of GnRHa to bring about an effective LH surge and subsequently to induce early luteal phase relative pituitary down-regulation. Luteolysis could be induced by diminished early luteal phase LH pulsatility, leading to prevention of OHSS. Our protocol calls for a single SC injection of 0.2 mg triptorelin (Decapeptyl; Ferring, Malmo, Sweden). We recorded no LH surge failures with this protocol and, of course, no clinically significant OHSS thus far (>1,000 patients, some of whom have been published).

**Benefits and Limitations**

As discussed above, GnRHa is an effective alternative to hCG in ART, particularly, when the threat of OHSS is imminent. In addition, it offers a more physiological stimulus for ovulation, combining both LH and FSH surges. Apparently, the presence of a midcycle FSH is not obligatory for successful ovulation, given the widespread use of hCG; hence it is not known whether the FSH surge associated with GnRHa is of any advantage.

Although a large body of evidence supports the role of this approach in OHSS prevention, none of the published papers reports the results of a bone fide prospective randomized study comparing GnRHa and hCG in terms of OHSS occurrence. Admittedly, without such a study, rapid dissemination of this approach cannot be anticipated. The applicability of such a study at this time is questionable because of ethical considerations.

A practical major limitation of GnRHa-induced ovulation is that it could not be effective in women with low gonadotropin reserve. Therefore, it is not applicable in IVF stimulation cycles during which pituitary down-regulation with a GnRH agonist is used. This protocol renders the pituitary unresponsive for induction of endogenous LH surge. Since GnRHa-based protocols have been used routinely by most IVF programs until recently, GnRHa-induced ovulation for OHSS prevention has not gained much popularity.

**GnRH Antagonists—New Opportunities**

The introduction of GnRH antagonists in controlled ovarian hyperstimulation protocols (26, 27) has presented new opportunities for novel stimulation protocols. A large (730 subjects) prospective randomized study (28) was carried out to compare long GnRHa (buserelin) and GnRH antagonist (ganirelix, orgalutran) protocols. The results suggest that ganirelix introduces a new treatment option for patients undergoing ovarian stimulation for IVF or intracytoplasmic sperm injection that is safe, short, and simple. The clinical outcome was good, and the ongoing pregnancy rate was within the range of pregnancy rates of a long-protocol GnRHa. This novel protocol also introduces new opportunities in the context of OHSS prevention. One possibility is to safely prevent spontaneous LH in high-risk patients with high doses of GnRH antagonist, waiting patiently for follicular demise and ovarian quiescence (29).

To effectively prevent OHSS, and to rescue the cycle at the same time, the quick reversibility of the antagonist-induced pituitary suppression can be advantageous by allowing the use of GnRHa for the purpose of ovulation triggering. This possibility has been assessed thus far in small-scale published studies (30, 31). From these reports it can be
deduced that the pituitary response to GnRH or GnRHa is preserved after GnRH antagonist–based follicular stimulation protocols. The extent of pituitary gonadotropin suppression depends on the dose used. Under the recommended minimal effective dose of GnRH antagonists (0.25 mg daily), it is most probable that ovulation could be safely and effectively triggered with a GnRHa.

This may become a significant potential advantage of GnRH antagonist–based controlled ovarian hyperstimulation protocols for IVF because it allows the clinician to choose the agent that will trigger ovulation. If OHSS is imminent, ovulation may be triggered with a GnRHa, eliminating any threat for significant OHSS.

GnRHa Ovulation Triggering in GnRH Antagonist Stimulation Protocols Prevents OHSS

This new treatment option for patients undergoing ovarian stimulation was used to eliminate the risk of developing OHSS in high responders. A preliminary report (32) describes the use of 0.2 mg triptorelin (decapetyl) to trigger ovulation in eight patients who underwent controlled ovarian hyperstimulation with recombinant FSH and concomitant treatment with the GnRH antagonist ganirelix for the prevention of premature LH surge. All patients were considered to have an increased risk for developing OHSS (at least 20 follicles ≥11 mm and/or serum E₂ at least 3,000 pg/mL). On the day of LH surge triggering, the mean number of follicles ≥11 mm was 25.1 ± 4.5 and the median serum E₂ concentration was 3,675 pg/mL (range, 2,980–7,670 pg/mL). After GnRHa injection, endogenous serum LH and FSH surges were observed with median peak values of 219 and 19 IU/L, respectively, measured 4 hours after injection. The mean number of oocytes obtained was 23.4 ± 15.4, of which 83% were mature (metaphase II). None of the patients developed any signs or symptoms of OHSS. These preliminary results clearly underline the effectiveness of this approach in OHSS prevention.

Summary

The physiologic basis and clinical applications of the use of GnRHa, rather than hCG, to induce the final stage of oocyte maturation and ovulation in gonadotropin-treated cycles were reviewed. A single midcycle dose of GnRHa is able to trigger a preovulatory LH/FSH surge, leading to oocyte maturation in women undergoing ovarian stimulation for IVF or induction of ovulation in vivo. The main advantage of this approach is the elimination of clinically significant OHSS. The mechanism of action involves complete quick and irreversible (even if pregnancy is achieved) luteolysis. Luteolysis can also be achieved surgically once severe OHSS has erupted (33), although it seems like a rather awkward solution once we have a simple medical means to achieve this same goal. Exogenous E₂ and P supplementation is necessary to compensate for the complete luteolysis. This approach will probably become a major advantage associated with the use of GnRH antagonist (rather than GnRHa down-regulation) in ART protocols. Its correct application is predicted to make severe OHSS a disease of the past.

References