Gonadotropin-Releasing Hormone Agonist Trigger: The Way to Eliminate Ovarian Hyperstimulation Syndrome—A 20-Year Experience

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ABSTRACT

Gonadotropin-releasing hormone agonist (GnRHa) trigger instead of human chorionic gonadotropin in the context of ovarian hyperstimulation syndrome (OHSS) prevention has been used for >20 years. In its first decade it did not gain popularity because it cannot work in GnRHa-based ovarian stimulation protocols. The introduction of GnRH antagonists has revolutionized our ability to eliminate OHSS completely because patients at high risk for OHSS can be triggered with GnRHa. This has been documented in randomized prospective studies, in which none of the patients randomized to the agonist trigger arm developed OHSS. In other words, GnRHa proved to be a potent tool that, truly remarkably, never fails. Although there is some debate concerning the clinical outcome of these cycles, data so far indicate that aggressive luteal support can ensure a good outcome. Moreover, the large number of frozen embryos in these cycles results in excellent per-oocyte retrieval pregnancy rates. In summary, GnRHa ovulatory trigger is the ultimate tool for complete OHSS prevention. GnRH antagonist-based ovarian stimulation protocols should be considered in OHSS high-risk patients so GnRHa trigger can be used if needed.

KEYWORDS: GnRH agonist, GnRH antagonisr, OHSS, in-vitro fertilization, ovarian stimulation

Ovarian hyperstimulation syndrome (OHSS) is the price we pay for our attempt to override nature's delicate balances that were created to assure single oocyte ovulation. Spontaneous OHSS does occur; however it is very rare. Natural cycle-based assisted reproductive technology (ART) was responsible for the birth of the first in vitro fertilization (IVF) infant, but it was abandoned because it is cumbersome and yields poor pregnancy rates. Therefore, gonadotropins (follicle-stimulating hormone [FSH] alone or a combination of FSH and luteinizing hormone [LH] activity) have been used for decades to stimulate the ovaries, particularly in the context of IVF. Typically, in these cycles human chorionic gonadotropin (hCG) is used as a surrogate to LH for the purpose of oocyte maturation and induction of ovulation. Given its significantly longer

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half-life (>24 hours versus 60 minutes for LH[1,2]), hCG administration results in a prolonged luteotrophic effect, characterized by the development of multiple corpora lutea and supraphysiological levels of estradiol (E_2) and progesterone (P). This sustained luteotrophic effect may result in the development of OHSS, still the most frequent and severe complication of ovarian stimulation treatments, a complication that can be *totally* prevented as described here.

THE SPONTANEOUS LH/FSH SURGE

The midcycle spontaneous LH surge is characterized by three phases: a rapidly ascending limb of 14-hour duration, a plateau of 14 hours, and a descending phase of 20 hours.[3] The parallel FSH surge is of lower amplitude. Serum E_2 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 the 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 E_2 as a luteal pattern of ovarian steroidogenesis is attained.

The Gonadotropin-Releasing Hormone Agonist–Induced LH/FSH Surge

Gonadotropin-releasing hormone agonist (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.[4–12] Based on these studies, it appears that a single administration of a GnRHa in a dose of 200 to 500 μg effectively and reliably triggers the required gonadotropin surge.[11,12] Preliminary experience[13] suggests that a single dose of 50 μg intranasal buserelin is the minimal effective dose to trigger ovulation.

The pituitary and ovarian responses to midcycle GnRHa injections in stimulated cycles were described previously.[8] The injection of GnRHa results in an acute release of LH and FSH. Serum LH and FSH levels rise for 4 and 12 hours, respectively, and are elevated for 24 to 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 E_2 levels during the first 12 hours after GnRHa administration. This is followed by a transient suppression of P biosynthesis and a gradual decline in E_2 levels during the 24 hours preceding follicle aspiration. After oocyte retrieval, a second rapid rise in P and continuous fall in E_2 are observed, reflecting normal transitions from follicular to luteal phase in ovarian steroidogenesis.

The Luteal Phase

Whereas the endogenous LH surge triggered by GnRHa is associated with an apparently normal early follicular-luteal shift in ovarian steroidogenesis, serum levels of E_2 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 depends on pituitary pulsatile LH secretion.[14] It is possible, therefore, that the presumed downregulation 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. Based on these considerations, it is prudent to support the luteal phase with P (and possibly E_2) in patients treated with midcycle GnRHa. Continued support during early pregnancy (until the luteal-placental shift) is required.

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[15] OHSS (e.g., ovarian enlargement, abdominal discomfort, and excessive steroid production) are an integral part of most cases of ovulation induction in IVF and are not clinically relevant. Effective ovulation is triggered with no risk of OHSS even in patients with extremely high E_2 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 of mild to moderate OHSS after nasal GnRHa trigger were reported by van der Meer et al.[16] Gerris et al[17] have also reported OHSS following this approach; however, they used *native* GnRH (and not *GnRHa*), resulting in successful ovulation triggering but without the critical gonadotropin suppression, which is the key element in preventing OHSS. Shoham et al[18] reported a personal communication of two OHSS cases.

Lastly, a group from Saudi Arabia has presented its large and impressive experience with this strategy.[19] Of 708 PCO, high responder IVF patients (mean E_2 on the day of ovulation triggering = 7817 pg/mL), ovulation was effectively triggered with GnRHa in 682 (96%).

One patient (0.1%) developed severe OHSS after being treated with hCG-based luteal support, probably in error, because the protocol dictated progesterone-only luteal support. In 18 patients the GnRHa-induced LH surge was judged as "inadequate," hCG was used, resulting in 11 cases (61%) 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 the inadequate LH surge may have to do with dose (too low) or route (intranasal) of the GnRHa administration. 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 downregulation. Luteolysis could be induced by diminished early luteal phase LH pulsatility, leading to prevention of OHSS. Our protocol calls for a single *subcutaneous* injection of 0.2 mg triptorelin (Decapeptyl; Ferring, Malmo, Sweden). We recorded no LH surge failures with this protocol, and not even one case of clinically significant OHSS out of hundreds of patients who were treated in our institution since 1987.

Benefits and Limitations

As discussed previously, 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 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 trigger is of any advantage.

A practical major limitation of GnRHa trigger is that it cannot be effective in women with a low gonadotropin reserve. Therefore, it is not applicable in IVF stimulation cycles during which pituitary downregulation with a GnRHa is used ("long protocol"). This protocol renders the pituitary unresponsive for induction of an endogenous LH surge. Because GnRHa-based protocols were used routinely by most IVF programs until the year 2000, GnRHa-induced ovulation for OHSS prevention has not gained much popularity.

GnRH Antagonists: New Opportunities

The introduction of GnRH antagonists (GnRH-ant) in controlled ovarian hyperstimulation protocols has opened new opportunities for novel stimulation protocols. A large prospective randomized study (730 subjects)[20] was performed to compare long GnRHa (buserelin) and GnRH-ant (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 secretion in high-risk patients with high-dose GnRH-ant, waiting patiently for follicular demise and ovarian quiescence.[21] To prevent OHSS effectively and to salvage the cycle at the same time, the quick reversibility of the antagonist-induced pituitary suppression can be of advantage by allowing the use of GnRHa as a trigger. This possibility was assessed in a randomized prospective multicenter study.[22] Two different GnRH agonists (0.2 mg triptorelin and 0.5 mg leuprorelin) were compared with hCG for triggering ovulation in a GnRH-ant-based (Orgalutran or Antagon) protocol for IVF. High responders (>25 follicles beyond 11 mm) were not included; hence agonist trigger in the context of OHSS prevention was not assessed. Luteal support was given by daily P administration. Both agonists triggered a successful LH surge (peak LH 4 hours post trigger). Interestingly, LH dynamics post trigger were similar to that reported without GnRH-ant pretreatment.[8] In other words, the routine daily dose of a GnRH-ant (ganirelix, 0.25 mg) does not blunt the effect of an agonist (given 12 hours apart) at the pituitary level. The three treatment groups (two agonists and hCG) had comparable number of oocytes retrieved, percentages of mature oocytes, fertilization rate, and clinical pregnancy rates.

Another randomized controlled study was performed to compare nonsupplemented luteal phase characteristics after three different triggers: recombinant hCG, recombinant LH, and GnRH agonist.[23] The area under the curve of progesterone secretion post agonist trigger was practically zero, reflecting complete luteolysis post agonist trigger. The concept of luteolysis post agonist was first coined by Casper and Yen[24] in 1979. They gave midluteal agonist to five normal volunteers. Luteolysis occurred as indicated by a fall in E_2 and P levels, followed by a shortened luteal phase.

To further characterize the presumed luteolytic process induced by midcycle injection of GnRHa, and to avoid confusion between endogenous biosynthesis and exogenous luteal support, we measured nonsteroidal luteal function markers, inhibin A, and pro-alphaC.[25] The agonist trigger caused a sharp decrease in these markers compared with patients who were treated with hCG. Pregnancy was not associated with a rise in the levels of the luteal markers. Therefore, we conclude that a GnRHa trigger results in complete and irreversible luteolysis. By the time endogenous hCG appears (if pregnancy is achieved), the corpora lutea are beyond

the point of "resuscitation;" therefore the production of endogenous sex steroids and associated OHSS mediators do not revive. OHSS is a serious and protracted disease if pregnancy is achieved. Therefore, it is of utmost importance to secure a trigger that will impede luteal activity before endogenous hCG appears. This is exactly what the agonist trigger does.

GnRHa Ovulation Triggering in GnRH-ant Stimulation Protocols Prevents OHSS

The tremendous strength of the proposed approach is also its weakness in terms of evidence-based medicine. Two groups performed randomized controlled studies with patients at high risk of OHSS.[26,27] The third group[28] used the donor-recipient model to elucidate the role of agonist trigger in terms of OHSS incidence and pregnancy rate while neutralizing the "endometrial factor." The main conclusion emerging from all three studies is clear: Agonist trigger prevents OHSS. In fact, none of the patients allocated to the GnRHa trigger arm in all three studies developed OHSS.

The Question of Pregnancy Rate following Agonist Trigger

Criticism of agonist trigger arose around the question of pregnancy rate. In normal responders, pregnancy rate following agonist trigger is comparable with that following hCG.[4,9,11] In contrast, two groups[29,30] published the results of randomized controlled studies in low-risk OHSS patients demonstrating a low pregnancy rate with agonist trigger. Poor clinical outcome probably has to do with deficient luteal support. The question of pregnancy rate in high responders was addressed in cycles during which hCG was used as the trigger. Pellicer et al[31] found that implantation rate was significantly higher in normal (18.5%) as compared with high (0%) responders. The researchers concluded that a different endocrine milieu between normal and high responders is detected by daily steroid measurements up to the preimplantation period, suggesting this difference could be responsible for an impaired implantation in high responder patients undergoing IVF. An increase in serum E_2 levels seems to be the cause of this difference. Simón et al[32] reached similar conclusions, stating that high serum E_2 concentrations on the day of hCG injection are detrimental to uterine receptivity without affecting embryo quality. Taken together, in the face of very high E_2 level on trigger day, freezing all embryos can be considered. Post-thaw pregnancy rates appear to be comparable to that of embryos obtained in normal responders. A "proof of concept" study by Griesinger et al[33] produced very promising results. Twenty high-risk OHSS patients ($\geq$20 follicles or E_2 $\geq$4000 pg/mL on trigger day) were triggered with agonist, all 2-pronucleate (2PN) oocytes were cryopreserved. None of the patients developed OHSS. Subsequent thaw cycles (mean of 2.3 embryos transferred) resulted in a 29.2% ongoing pregnancy rate. Each patient had an average of 7.4 2 PN cryopreserved, allowing for an average of three subsequent thaw cycles. With a 29.2% ongoing pregnancy rate per thaw cycle, each patient has an excellent chance of achieving an ongoing pregnancy following a single oocyte retrieval, with complete safety as far as OHSS is concerned.

Take-Home Messages

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 complete elimination of clinically significant OHSS. The application of this trigger in high responders requires a responsive pituitary. Therefore, it is not applicable in GnRHa-based cycles during which pituitary downregulation is achieved. GnRH-ant-induced competitive inhibition of the pituitary GnRH receptors is easily reversible with a GnRHa. In fact, a major reason to use GnRH-ant in ovarian stimulation is to maintain the option of agonist trigger if needed. A clinical protocol for the high responder is as follows:

- Start stimulation with 100 to 150 IU recombinant FSH.
- Start antagonist on day 6 of stimulation.
- Trigger with 0.2 mg triptorelin or 0.5 leuprorelin instead of hCG if ovarian response is in the OHSS danger zone.
- Start luteal support with E_2 and P on day following oocyte retrieval if fresh transfer is planned. Do not administer any support if all embryos are to be frozen.

This protocol will prevent the development of OHSS, every time, no exceptions.

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