Review article

GnRH agonist trigger in modern reproductive medicine practice – *when, why, and how?*

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Abstract

The use of gonadotropin-releasing hormone (GnRH) antagonist protocols in assisted conception is a major advance in modern reproductive medicine practice. Specifically, the application of GnRH agonist (GnRHa) as the final trigger for oocyte maturation in cycles where GnRH antagonist has been used is associated with a significant reduction in the risk of developing one of the most serious iatrogenic complications of assisted conception, ovarian hyperstimulation syndrome. GnRHa trigger has been shown to be as effective as human chorionic gonadotropin trigger with respect to oocyte yield and maturity in both autologous and donor cycles in multiple studies. This trigger, however, results in poor corpus luteum development and consequently luteal phase dysfunction and impaired endometrial receptivity. In this review, we address the indications, contraindications, outcomes, and practical considerations when using the GnRHa trigger.

Keywords: cryopreservation, GnRH agonist, GnRH antagonist, OHSS, oocyte donors

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INTRODUCTION

The use of gonadotropin-releasing hormone (GnRH) antagonist protocols in assisted conception is a major advance in modern reproductive medicine practice. The difference between GnRH agonist and antagonist is lack of receptor downregulation in antagonist cycle, hence the gonadotrophs remain sensitive to GnRH as there is no secretory exhaustion.

When gonadotropin-releasing hormone agonist (GnRHa) is used as a trigger in a GnRH antagonist cycle, it displaces the antagonist from the GnRH receptor. GnRHa binding to the receptor induces luteinizing hormone (LH) and follicle-stimulating hormone (FSH) surge. This surge resembles the physiologic surge in some respects, but there are also important differences. The GnRHa-induced LH surge is of shorter duration, with an ascending limb of 4 hours and a descending limb of 20 hours. In comparison, in the spontaneous cycle, the LH surge reaches a peak in 14 hours, followed by a plateau phase of 14 hours and a descending phase of 20 hours, with a total duration of around 48 hours[1] [Figure 1]. This shorter duration of GnRHa-induced LH surge results in quick luteolysis and therefore, is beneficial in minimizing the risk of ovarian hyperstimulation syndrome (OHSS).[2]

There are significant differences between the GnRHa-induced surge and a human chorionic gonadotropin

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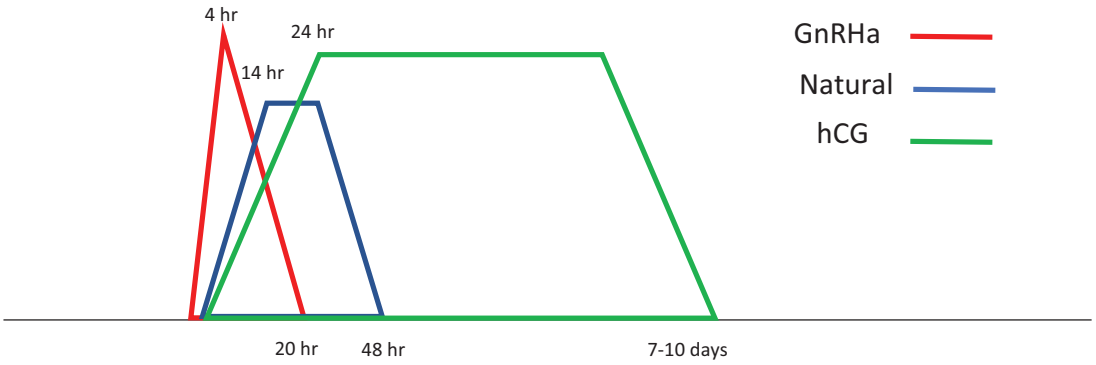

FIGURE 1: Time profile of LH surge in natural and GnRHa trigger. hCG level is shown for comparison.

(hCG) trigger. With hCG trigger, there is a lack of FSH, more marked luteotropic effect and prolonged duration of action. The half-life of exogenous hCG is 24 hours, and it takes around 7 to 10 days for complete clearance. This results in a prolonged luteotropic effect as compared to both the midcycle physiological LH surge and the GnRHa-induced surge.

The follicular fluid following GnRHa trigger is noted to have higher LH and FSH levels than those after hCG trigger due to combined surge of both gonadotropins. Progesterone levels are reduced by 25%. Vascular endothelial growth factor (VEGF) levels are significantly reduced, and expression of VEGF mRNA in the granulosa cells is decreased as compared to hCG trigger. VEGF is believed to be the critical mediator of increased vascular permeability that is responsible for OHSS, and reduced levels of VEGF after GnRHa trigger may play a major role in the lower risk of OHSS with this trigger compared to hCG.

The natural ovulatory surge during midcycle consists of both LH and FSH surge. Both hormones have a crucial role in midcycle events leading to successful ovulation and luteal function (see box 1 and box 2). The GnRHa-induced surge is similar in this respect to the natural surge, whereas hCG trigger lacks an FSH component.

Role of LH surge
1. Resumption of meiosis + release of 1st polar body
2. Shift towards progesterone induced luteinization
3. Extrusion of oocyte by proteolytic digestion of follicular wall
4. Improving endometrial receptivity

Role of FSH surge (not completely elucidated)
1. Oocyte maturation
2. Function of oocyte-cumulus complex and facilitation of its detachment from the follicle wall
3. Generation of LH receptors on granulosa cells

Indications

Though GnRHa trigger was devised primarily for prevention of OHSS, any patient who is suitable for segmentation of IVF cycle, that is, for elective cryopreservation, is a potential candidate for this measure.

(1) High risk for OHSS – based on ovarian reserve parameters and/or history of PCOS/OHSS in the past
(2) Oocyte donors
(3) Elective cryopreservation
   (a) Fertility preservation for medical reason
      (1) Cancer
      (2) Transgender
   (b) Fertility preservation for social reasons
   (c) Preimplantation genetic testing

Contraindications

Patients who would not mount a gonadotropin response to GnRH agonist

(1) Hypothalamic dysfunction, for example, low BMI, low basal LH
(2) Long-term suppression of hypothalamus/pituitary leading to receptor desensitization, for example, prolonged oral contraceptive pill usage, prolonged administration of GnRH agonist in cases of endometriosis/adenomyosis.

Practical Considerations

Dose

(1) Leuprolide – Different doses of subcutaneous leuprolide have been used in literature and range from 0.5 to 4 mg[3], and some studies have used two doses 12 hours apart.[4] A single dose of 1 mg is effective for optimal mature oocyte yield.[5]
(2) Triptorelin – A randomized dose finding study of 0.2, 0.3, and 0.4 mg triptorelin in oocyte donors showed similar rates of mature oocytes and good-quality embryos regardless of dose.[6]

(3) Buserelin – A dose of 50 mcg intranasal buserelin is the effective minimal dose for triggering.[7] Subcutaneous buserelin has been used in variable doses in the literature; in our practice a dose of 2 mg has been associated with excellent results.[8-10]

Timing

The GnRHa trigger is usually prescribed 8 to 12 hours after the last antagonist dose in clinical practice. In a retrospective cohort study of 53 patients undergoing GnRH antagonist-based *in vitro* fertilization (IVF) cycles, in whom a GnRHa was used for final ovulation triggering, the mean time interval between the last GnRH antagonist dose and GnRHa trigger was 4.6 ± 2.7 hours (range 1–12 hours). The antagonist–agonist interval was not associated with difference in oocyte recovery rate, metaphase II oocyte rate or treatment outcomes, after adjusting for the women's age and body mass index.[11]

Dual trigger

Addition of hCG to GnRHa trigger (discussed in detail in later section) has been used to enable fresh embryo transfer. It should be kept in mind that even a low dose of hCG can increase the risk of OHSS, and this should be avoided in women at high risk of OHSS. There has been conflicting results by various studies, regarding effect of dual trigger and fertility treatment outcomes in normal responders. The randomized controlled trial (RCT) conducted by Eftekar *et al.* and Mahajan *et al.* has shown no benefit of dual trigger over hCG and assisted conception outcomes; however, another RCT by Haas *et al.* favors dual trigger and its effect on final oocyte maturation results.[12-14] A recent meta-analysis of various RCT has concluded the beneficial effect of dual trigger over the live birth rate in comparison to traditional hCG trigger.[15] GnRH agonist trigger combined with hCG has been associated with improved outcome and more mature oocytes in poor responder.[16,17] It has also been suggested in women with a poor ovarian response, and as a method of reducing the risk of empty follicle syndrome.[8]

WHAT NEXT?

The median duration of the luteal phase after GnRHa trigger may be as short as 9 days as compared to 13 days after hCG trigger. Potential reasons for early luteolysis include the following:

(1) Short duration of LH surge – sufficient to induce maturation of oocyte but not sufficient to induce and maintain adequate corpora lutea
(2) After trigger (flare effect), GnRHa may partially downregulate pituitary
(3) Supraphysiological levels of progesterone and estrogen from ovarian stimulation also suppress endogenous LH release

A Cochrane review suggested that GnRH agonist as a final oocyte maturation trigger in fresh autologous cycles is associated with lower live birth rate, lower ongoing pregnancy rate (pregnancy beyond 12 weeks), and a higher rate of early miscarriage (less than 12 weeks).[18]

Due to this, segmentation of the IVF cycle with elective cryopreservation is most often used following a GnRHa trigger. However, fresh embryo transfer modified luteal support has also been studied, and in this section we assess both approaches.

Cryopreservation of embryos followed by Frozen Embryo Replacement	Fresh transfer-Strategies for modifying luteal phase
	1. Oestrogen and Progesterone (E + P) 2. hCG a. Dual trigger b. Adjuvant hCG at the time of ultrasound-guided oocyte retrieval (USOR) 3. Recombinant LH 4. Luteal coasting 5. GnRHa luteal support

CRYOPRESERVATION FOLLOWED BY FER

GnRHa trigger followed by segmentation (elective cryopreservation) of IVF cycle could potentially result in an "OHSS free clinic." This needs to be weighed up with success rates of frozen embryo replacement. Not all IVF units have optimal cryopreservation program, which is crucial for success of segmentation.

A systematic review and meta-analysis by Roque *et al.* in 2019 showed a higher live birth rate in elective frozen embryo transfer (eFET) cycles than fresh cycles in hyper responders (RR = 1.16, 95% CI 1.05–1.28). The same meta-analysis showed that the risk of moderate/severe OHSS was significantly lower with eFET than fresh cycle (RR = 0.42, 95% CI 0.19–0.96). This adds support to the concept that OHSS prevention can be accomplished without sacrificing overall outcome, by judicious use of GnRH agonist trigger and elective freeze-all.[19]

Recently, in a RCT, Santos-Riberio *et al.* compared, freeze-all strategy versus agonist trigger with low-dose hCG for luteal phase support and fresh embryo transfer, in IVF/ICSI for high responders, following GnRHa trigger. Cases of significant OHSS occurred only in the fresh transfer group, and pregnancy rates were similar between both groups. Hence, from the point of view of OHSS prevention, elective cryopreservation of all embryos is safer than even considering a small dose of hCG for fresh embryo transfer.[20]

FRESH TRANSFER WITH MODIFIED LUTEAL SUPPORT

(1) Estrogen and Progesterone Support –
Intensive support using 50 mg I.M. progesterone and three 0.1 mg estradiol patches replaced alternate day has been described by Engmann *et al.* in an RCT of 66 PCOS/high responder patients. In GnRHa trigger group, they recommended starting intensive support and monitoring serum levels of progesterone and estrogen. Based on serum levels, dose of I.M. progesterone was increased up to 75 mg daily with addition of micronized vaginal progesterone daily as needed to maintain serum progesterone level above 20 ng/mL. Similarly, estrogen patches were increased to four 0.1 mg patches every alternate day, with addition of oral micronized estrogen (2–8 mg) to maintain serum levels above 200 pg/mL. This study showed that there was 53% ongoing pregnancy rate in cycles with intensive luteal phase support after GnRHa trigger as compared to 48.3% in cycles with hCG trigger and standard luteal support.[21]

(2) hCG –
   (a) Dual trigger – A small dose of hCG (1000–2500 IU) along with GnRHa trigger followed by intensive steroid luteal support has been used to serve as "back up" to prevent GnRHa trigger failure.[22]
   (b) Adjuvant hCG at the time of USOR – Although rapid luteolysis occurs after GnRHa trigger, granulosa/luteal cells maintain similar functionality and viability within the first 2 days after trigger as compared with hCG trigger, hence remain responsive if further hCG is given. A single bolus of 1500 IU hCG has been described by Humaidan and colleagues, followed by standard luteal phase support using estrogen and progesterone, to give similar pregnancy rates as hCG trigger cycles.[23] However, the study by Santos Ribeiro[20] should make clinicians cautious about even a small exposure to hCG in high-risk patients.

(3) Recombinant LH –
This could be considered for luteal phase supplementation, perhaps with benefit of shorter half-life than hCG to further minimize OHSS risk. A small proof-of-concept study has been done with 18 patients in study group who received GnRHa trigger followed by six doses of 300 IU rLH every second day during luteal phase along with standard LPS, and control group with 17 patients who received 6500 IU of hCG followed by standard LPS. All patients underwent single blastocyst transfer. Similar implantation rates (26.7% vs. 25%) were seen and no OHSS cases were reported.[24]

(4) "Individualized" Luteal Support –
Lawrence *et al.* suggested that based on assessment of oestradiol (E2) – and P4–levels 48 hours after oocyte-pick-up, procedure demonstrate clearly that luteolysis after GnRH-agonist trigger is individual-specific, even in high-responder patients with the same number of oocytes. Hence, luteal phase support may be individualized based on severity of luteolysis with the focus on avoiding unnecessary administration of hCG, bearing the risk for development of OHSS.[25]

(5) GnRHa Luteal Support –
In a prospective trial by Wiser *et al.*, patients exhibiting oestradiol concentrations of over 2500 pg/mL after use of a GnRH agonist for triggering ovulation were initially randomized to GnRH agonist luteal support (0.1 mg subcutaneously every other day, starting on day 3 after embryo transfer) or to a control group supported by 80 μg of recombinant HCG on day 3 after embryo transfer. All patients underwent a day 5 blastocyst transfer. Randomization to the hCG luteal support was stopped owing to two cases of OHSS and the study was continued solely with GnRH agonist luteal support. The study included 39 women in the repeated GnRH agonist luteal support group and seven in the hCG micro dose group. There were no cases of OHSS among patients supported by a GnRH agonist, and no other adverse events were recorded. There were no cases of bleeding before the pregnancy test, and hence no cases of an insufficient luteal phase. A clinical pregnancy rate of 43.6% was achieved with GnRH agonist luteal support. They concluded that repeated doses of GnRH agonist every other day as a method of luteal support provided safe and effective luteal support for women who underwent GnRH agonist triggering in a GnRH antagonist IVF cycle.[26]

CAUTION AND SAFETY

OHSS despite GnRHa trigger

Rarely, cases of severe OHSS have been described even after the use of GnRHa trigger without hCG exposure.[27-29] Activating mutations of FSH receptor could predispose to OHSS in such cases. It should also alert physician to search for either an inadvertent administration of exogenous hCG, or the endogenous secretion of hCG by pregnancy, for example, extra uterine pregnancy, or as part of a paraneoplastic syndrome.[30]

Empty follicle syndrome

It has a total prevalence of 0.6% to 7%. It could either be false empty follicle syndrome (FEFS) due to fault in drug administration/pharmacological issues or genuine empty follicle syndrome (GEFS) due to intrinsic cause. GEFS constitutes a small proportion of 0% to 1.1%. In GEFS, the level of hCG or LH/progesterone (depending on the type of trigger) is adequate, whereas in FEFS it is low. The incidence of GEFS is similar following hCG and GnRHa trigger. Kummer *et al.* found that there are no clear serum predictors of oocyte yield, but post trigger LH and progesterone measurement strongly correlated with total oocytes and mature oocytes retrieved. All cases of EFS had LH $<$ 15 IU/L and progesterone $<$ 3.5 ng/mL measured 8 to 12 hours after trigger.[5]If there is no LH surge/progesterone rise after GnRHa trigger, repeat trigger with hCG and USOR after 35 hours has shown good oocyte recovery. If no oocytes are retrieved after unilateral follicle aspiration, one approach that we have found useful is to stop and retrigger with hCG followed by oocyte retrieval from other ovary 34 to 36 hours later, unless the clinician judges the risk of OHSS to be too high for hCG trigger.

Safety

Budinetz *et al.* found no significant difference in the rate of congenital anomalies, maternal complications, or minor and major neonatal complications between GnRHa and hCG triggers.[31]

PRACTICE POINTS

(1) GnRH agonist is *only* a suitable trigger in the antagonist cycle.
(2) It reduces the risk of early OHSS to very low, and coupled with elective cryopreservation can potentially eliminate OHSS.
(3) It may improve the quality of oocytes in cases with low ovarian reserve and those with a history of poor fertilization (due to concomitant FSH surge).
(4) It is *not* a suitable option in cases of HPO dysfunction.
(5) Luteolysis following GnRH agonist trigger demands extra luteal support if proceeding with fresh transfer.

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Conflicts of interest

The authors report no conflicts of interest.

Commentary

Gonadotropin-releasing hormone agonist (GnRh-a) when used as a trigger (for final maturation) has known to eliminate early-onset ovarian hyper-stimulation syndrome (OHSS). Severe OHSS is an iatrogenic complication in assisted reproductive technique (ART) in approximately 2% of patients, adding to morbidity and mortality especially as the number of ART cycles continues to be on the rise every year. Preventing OHSS while giving the best pregnancy outcome is the goal in ART. Luteinising Hormone (LH) surge amplitude following GnRh trigger is very much similar to that of natural menstrual cycle. However, in GnRh agonist protocol one cannot employ GnRh agonist trigger because the receptors have been desensitised. LH surge of agonist trigger is short lived and in fresh autologous cycle there is early involution of corpora luteum that plays a detrimental role for the implanting embryo but helps in preventing OHSS.

Results from clinical trials have shown a lower pregnancy rate with GnRh agonist trigger compared with the traditional human chorionic gonadotropin (HCG) trigger as a result of insufficient stimulation of corpora luteum formation by agonist trigger leading to luteal phase deficiency. It needs to be emphasised that GnRh agonist trigger has no detrimental effect on embryo quality as seen in donor oocyte studies. Several strategies have brought down the rates of OHSS; however, there exists no strategy better than freeze all and GnRh agonist trigger to completely prevent OHSS. Thus, GnRh agonist trigger has tremendous potential for future research.

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