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Review of GNRH Agonist and HCG for Ovulation Triggering and Final Oocyte Maturation in IVF

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Abstract: *Ovulation triggering and final oocyte maturation represent critical stages in in-vitro fertilization treatment because the timing and physiological characteristics of the trigger influence oocyte maturity, fertilization, embryo development, and the risk of ovarian hyperstimulation syndrome. Human chorionic gonadotropin has traditionally been used as the principal trigger because its biological activity resembles that of luteinizing hormone. However, its prolonged half-life may increase the risk of excessive luteal stimulation and OHSS, particularly in patients with a high ovarian response. Gonadotropin-releasing hormone agonist triggering provides an alternative approach in GnRH antagonist cycles by inducing an endogenous LH and follicle-stimulating hormone surge.*

Keywords: GnRH agonist, ovulation trigger, final oocyte maturation, IVF, OHSS, luteal phase support, ovarian stimulation.

I. INTRODUCTION

In controlled ovarian stimulation for IVF, multiple follicles are developed simultaneously through exogenous gonadotropin administration. Because spontaneous ovulation must be prevented until oocyte retrieval is planned, final follicular maturation is artificially induced using a pharmacological trigger. The trigger is generally administered when an appropriate cohort of follicles has developed, followed by transvaginal oocyte retrieval approximately 34–36 hours later. The final maturation process involves resumption of meiosis, cumulus expansion, changes in steroidogenesis, and preparation of the oocyte for fertilization. Therefore, selection of the trigger is a major component of IVF treatment strategy.

Historically, hCG has been widely used because it binds to the LH receptor and produces a prolonged LH-like signal. Although effective, the extended biological activity of hCG can produce sustained stimulation of ovarian LH receptors and increase the risk of OHSS. This concern is particularly important among women with polycystic ovary syndrome (PCOS), high anti-Müllerian hormone concentrations, high antral follicle counts, or large numbers of developing follicles. The introduction of GnRH antagonist protocols provided an important opportunity to use GnRH agonists for final oocyte maturation. In an antagonist cycle, administration of a GnRH agonist can stimulate the pituitary to release endogenous LH and FSH. The resulting surge more closely resembles the physiological gonadotropin surge than the prolonged stimulation generated by hCG. This approach has substantially changed the management of patients at increased risk of OHSS.

The purpose of this review is to compare GnRH agonist and hCG triggering with particular emphasis on mechanism of action, oocyte maturation, embryological outcomes, OHSS risk, luteal-phase consequences, clinical applications, and limitations.

II. PHYSIOLOGICAL BASIS OF FINAL OOCYTE MATURATION

Final oocyte maturation begins after the LH surge. The preovulatory LH surge stimulates a cascade of events within the dominant follicle, including cumulus expansion, resumption of meiosis, nuclear maturation from the germinal-vesicle stage toward metaphase II, follicular progesterone production, and enzymatic changes associated with follicular rupture.

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In IVF, the natural LH surge is replaced by an induced hormonal signal. The objective is not simply to cause follicular rupture but to obtain mature metaphase-II oocytes at the time of retrieval. Both hCG and GnRH agonists can initiate this process, but they do so through different endocrine mechanisms.

III. HCG AS AN OVULATION TRIGGER

hCG is structurally related to LH and acts primarily through the LH/hCG receptor. Following administration, it produces a prolonged LH-like effect because of its relatively long half-life. This prolonged stimulation effectively supports final follicular maturation and ovulation.

The principal advantage of hCG is its reliability. It has been used extensively in conventional IVF and is associated with effective oocyte maturation and retrieval. However, its prolonged activity also stimulates luteinized granulosa cells after retrieval. In patients with a large number of corpora lutea, this can increase vascular permeability and contribute to OHSS. Consequently, hCG triggering requires careful consideration of ovarian response. A standard hCG trigger may be inappropriate for patients with very high follicular recruitment because the risk of OHSS can become clinically significant.

IV. GNRH AGONIST AS AN OVULATION TRIGGER

GnRH agonist triggering is generally possible when pituitary responsiveness is preserved, particularly in cycles using a GnRH antagonist. Administration of a GnRH agonist produces an initial pituitary stimulation followed by an endogenous LH and FSH surge.

The resulting gonadotropin surge is shorter in duration than the prolonged LH-receptor stimulation caused by hCG. This difference is clinically important because the shorter exposure reduces excessive luteal stimulation and markedly lowers the risk of OHSS.

However, the short endogenous gonadotropin surge can also result in insufficient luteal support. Following GnRH agonist triggering, endogenous LH concentrations decline rapidly because of pituitary desensitization. Therefore, patients undergoing fresh embryo transfer generally require an intensified or modified luteal-support strategy.

V. COMPARISON OF GNRH AGONIST AND HCG TRIGGERS

Parameter	GnRH Agonist Trigger	hCG Trigger
Primary mechanism	Induces endogenous LH/FSH surge	Direct LH-receptor stimulation
Duration of action	Relatively short	Prolonged
Final oocyte maturation	Effective	Effective
OHSS risk	Very low when appropriately used	Higher, especially in high responders
Luteal function	Relatively deficient without additional support	More sustained luteotropic effect
Fresh embryo transfer	Requires intensive luteal support	Conventional luteal support generally sufficient
High-risk OHSS patients	Particularly useful	Generally less desirable
Low responders	May be less suitable if pituitary response is inadequate	May be useful
Antagonist cycles	Particularly applicable	Applicable
Freeze-all strategy	Highly compatible	Also compatible
Main limitation	Luteal-phase deficiency	OHSS risk
Clinical selection	Individualized according to ovarian response	Individualized according to ovarian response

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VI. EFFECT ON OOCYTE MATURITY

Both triggers can achieve high rates of mature metaphase-II oocytes when appropriately timed. GnRH agonist triggering has demonstrated effective final oocyte maturation in antagonist cycles, although outcomes may vary according to ovarian response, trigger timing, gonadotropin exposure, and patient characteristics.

The quality of the oocyte depends on more than nuclear maturation alone. Cytoplasmic maturation and synchronization between nuclear and cytoplasmic processes are also important for successful fertilization and subsequent embryo development. Therefore, an ideal trigger should produce adequate maturation without excessive endocrine stimulation.

VII. GNRH AGONIST TRIGGER AND OHSS PREVENTION

One of the most important clinical benefits of GnRH agonist triggering is prevention of OHSS in susceptible patients. OHSS is associated with increased vascular permeability, fluid shifts, ovarian enlargement, hemoconcentration, and, in severe cases, thromboembolic and respiratory complications.

The risk is particularly relevant among women with PCOS and those who develop a large number of follicles during stimulation. Because GnRH agonist triggering produces a shorter endogenous LH surge than hCG, it substantially reduces the persistent luteotropic stimulation that contributes to late-onset OHSS.

For this reason, GnRH agonist triggering is widely regarded as a major component of OHSS-risk reduction in antagonist-based IVF protocols.

VIII. LUTEAL-PHASE CONSEQUENCES OF GNRH AGONIST TRIGGERING

The major limitation of GnRH agonist triggering is luteal-phase insufficiency. The endogenous LH surge is short-lived, and the subsequent fall in LH can lead to inadequate progesterone production by the corpus luteum. This problem is particularly important when fresh embryo transfer is planned.

Several strategies have therefore been developed, including intensive progesterone administration, additional estradiol supplementation, low-dose hCG rescue, or modified luteal support protocols. In patients at substantial OHSS risk, a freeze-all strategy can eliminate the need for fresh transfer and allows embryo transfer to occur later in a hormonally controlled cycle.

IX. HCG TRIGGER AND CLINICAL UTILITY

Despite the increasing use of GnRH agonist triggers, hCG remains clinically relevant. Its predictable and prolonged LH-receptor activity makes it effective for inducing final maturation. It may be particularly useful in patients who have a low risk of OHSS or when a strong luteal stimulus is desirable.

However, hCG should be used cautiously in patients with high ovarian response. The cumulative risk associated with high follicular numbers means that the trigger should be selected according to individual ovarian characteristics rather than by a universal protocol.

X. EMBRYOLOGICAL AND PREGNANCY OUTCOMES

The effect of trigger choice on reproductive outcomes is influenced by whether fresh or frozen embryo transfer is performed. In fresh cycles, GnRH agonist triggering can be associated with lower implantation or pregnancy outcomes if luteal support is inadequate. This does not necessarily indicate inferior oocyte quality; rather, it reflects the endocrine consequences of the trigger.

When embryos are cryopreserved and subsequently transferred in an appropriately prepared endometrium, the adverse luteal consequences associated with GnRH agonist triggering can be minimized. Thus, the clinical strategy increasingly separates ovarian stimulation and embryo transfer when this approach is appropriate.

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XI. SAFETY CONSIDERATIONS

Safety is central to trigger selection. hCG is effective but has a recognized association with OHSS, especially in women with a high ovarian response. GnRH agonist triggering considerably reduces this risk but requires careful management of the luteal phase.

Other considerations include the possibility of inadequate response in patients with impaired pituitary function, inappropriate timing of trigger administration, and the need for individualized luteal support. Therefore, ovarian reserve markers, follicular development, estradiol levels, previous response to stimulation, and the planned embryo-transfer strategy should all be considered.

XII. CLINICAL DECISION-MAKING

Trigger selection should be individualized. A GnRH agonist trigger is particularly attractive in GnRH antagonist cycles involving patients with high ovarian response or substantial OHSS risk. Conversely, hCG may remain appropriate in patients with lower ovarian response and low OHSS risk.

The decision should also consider whether the treatment plan involves fresh embryo transfer or cryopreservation. GnRH agonist triggering combined with a freeze-all approach is especially useful when OHSS prevention is a major objective.

Table 2. Practical Clinical Selection of Trigger

Clinical Situation	Preferred Consideration
High ovarian reserve	GnRH agonist trigger
PCOS/high OHSS risk	GnRH agonist trigger
Large follicular cohort	GnRH agonist trigger
Freeze-all strategy	GnRH agonist trigger is highly suitable
Low OHSS risk	hCG may be considered
Low/normal ovarian response	hCG may be useful
Fresh transfer after GnRH agonist	Intensive luteal support required
High risk of luteal insufficiency	Modified luteal-support strategy
Pituitary suppression/nonresponsive pituitary	hCG may be more appropriate
Need to minimize OHSS	GnRH agonist preferred

XIII. ADVANTAGES AND LIMITATIONS

1. GnRH Agonist Trigger

Advantages

1. Markedly reduces OHSS risk.
2. Produces an endogenous LH/FSH surge.
3. Particularly useful in antagonist protocols.
4. Compatible with freeze-all strategies.
5. Useful for patients with high ovarian response.

Limitations

1. Causes rapid luteolysis.
2. Requires enhanced luteal support for fresh transfer.
3. May not be suitable in all ovarian stimulation protocols.
4. Requires adequate pituitary responsiveness.

2. hCG Trigger

Advantages

1. Established and predictable clinical efficacy.
2. Produces effective final oocyte maturation.

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3. Provides prolonged luteotropic stimulation.
4. Can be useful in low-risk patients and selected low responders.

Limitations

1. Greater OHSS risk.
2. Prolonged biological activity.
3. Less attractive for patients with very high ovarian response.
4. Requires careful dose and patient selection.

XIV. OVERALL EVIDENCE SYNTHESIS

The available clinical evidence supports a complementary rather than absolute view of GnRH agonist and hCG triggering. GnRH agonist triggering provides a major safety advantage in patients at increased risk of OHSS, while hCG remains an effective and clinically useful trigger in appropriately selected patients.

The most important distinction is not simply whether one trigger produces more mature oocytes than the other. Rather, the choice affects the endocrine environment after retrieval, particularly luteal function. GnRH agonist triggering shifts the clinical focus from prolonged luteotropic stimulation toward OHSS prevention, while hCG prioritizes sustained LH-receptor activity at the cost of greater OHSS risk.

XV. CONCLUSION

GnRH agonist and hCG triggers are effective pharmacological approaches for inducing final oocyte maturation in IVF, but their physiological effects differ substantially. hCG provides prolonged LH-like activity and reliable maturation but can increase OHSS risk, particularly in high responders. GnRH agonist triggering produces a short endogenous LH/FSH surge and offers a significant reduction in OHSS risk, making it especially valuable in GnRH antagonist cycles involving women with high ovarian response.

Its principal limitation is luteal-phase insufficiency, which must be addressed through individualized luteal support or, in appropriate cases, cryopreservation and subsequent frozen embryo transfer. Consequently, trigger selection should be individualized according to ovarian reserve, stimulation response, OHSS risk, pituitary responsiveness, and embryo-transfer strategy. Rather than replacing hCG universally, GnRH agonist triggering should be viewed as an important component of personalized IVF treatment and OHSS-prevention strategies.

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