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Randomised Controlled Evidence Comparing GNRH Agonist and HCG for Final Oocyte Maturation in IVF

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Abstract: *Final oocyte maturation is a critical step in in-vitro fertilization (IVF), traditionally achieved using human chorionic gonadotropin (hCG). Gonadotropin-releasing hormone agonist (GnRH-a) triggering has emerged as an alternative, particularly in patients receiving GnRH antagonist stimulation protocols and those at increased risk of ovarian hyperstimulation syndrome (OHSS). This proposed randomized controlled study compares the effectiveness and safety of GnRH-a and hCG for final oocyte maturation in women undergoing IVF. A total of 120 eligible women would be randomly allocated into two equal groups: Group A would receive a GnRH agonist trigger and Group B would receive an hCG trigger.*

The principal outcomes would include the number of retrieved oocytes, mature oocytes, fertilization rate, embryo quality, clinical pregnancy, ongoing pregnancy, live birth, and incidence of moderate-to-severe OHSS. Statistical analysis would involve independent-samples t-tests or Mann–Whitney U tests for continuous variables and chi-square or Fisher's exact tests for categorical variables.

Existing randomized evidence indicates that GnRH-a triggering markedly reduces OHSS risk but may produce inferior pregnancy outcomes when used alone in fresh autologous cycles. Consequently, the selection of trigger should consider ovarian response, OHSS risk, embryo-transfer strategy, and luteal-phase support. Current clinical guidance recommends GnRH-a triggering as a first-line strategy for reducing moderate-to-severe OHSS, with adequate luteal support when fresh embryo transfer is planned.

Keywords: IVF, GnRH agonist, hCG, final oocyte maturation, oocyte retrieval, OHSS, pregnancy rate, randomized controlled trial.

I. INTRODUCTION

In-vitro fertilization involves controlled ovarian stimulation followed by final oocyte maturation, transvaginal oocyte retrieval, fertilization, embryo culture and embryo transfer. Final oocyte maturation is normally induced approximately 34–36 hours before oocyte retrieval. Human chorionic gonadotropin has historically been used because its biological activity resembles luteinizing hormone and provides a sustained stimulus for luteinization and meiotic maturation. However, prolonged hCG activity can increase the risk of ovarian hyperstimulation syndrome, particularly among women with a high ovarian response.

GnRH agonist triggering provides an alternative mechanism. In patients undergoing GnRH antagonist protocols, administration of a GnRH agonist stimulates the pituitary to produce an endogenous LH/FSH surge. This surge is shorter than the biological activity of hCG and consequently can reduce ovarian exposure to luteotropic stimulation. Randomized evidence has demonstrated a substantial reduction in moderate-to-severe OHSS with GnRH agonist triggering. However, when GnRH agonist is used alone in fresh autologous cycles, luteal-phase dysfunction may result in lower ongoing pregnancy and live-birth rates.

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The American Society for Reproductive Medicine recommends GnRH agonist triggering as a first-line strategy for reducing moderate-to-severe OHSS and recommends adequate luteal support when a fresh embryo transfer is planned.

II. METHODOLOGY

1. Research Design

A prospective, parallel-group, randomized controlled trial would be used.

2. Study Population

The proposed population would comprise women undergoing IVF/ICSI using a GnRH antagonist controlled ovarian stimulation protocol.

3. Proposed Sample

A total of 120 participants would be randomized equally:

Group A: 60 participants — GnRH agonist trigger

Group B: 60 participants — hCG trigger

The sample size should ultimately be calculated from the primary endpoint, expected effect size, statistical power, significance level and anticipated loss to follow-up rather than assumed solely for illustration.

III. INCLUSION CRITERIA

Women would be eligible if they:

1. were undergoing IVF/ICSI;
2. were within the predefined reproductive-age range;
3. were treated using a GnRH antagonist stimulation protocol;
4. had adequate follicular development for final maturation;
5. consented to participation.

5. Exclusion Criteria

Participants would be excluded for:

1. severe systemic disease affecting fertility treatment;
2. significant ovarian pathology;
3. use of donor oocytes;
4. inability to provide informed consent;
5. contraindication to either trigger;
6. major protocol deviation.

6. Randomization

Eligible participants would be assigned using computer-generated random allocation. Allocation concealment should be maintained using sequentially numbered sealed envelopes or an equivalent centralized system.

7. Intervention

Group A: GnRH agonist trigger according to the IVF centre's validated clinical protocol.

Group B: hCG trigger according to the centre's standard clinical protocol.

The exact drug, dose and timing should be prespecified in the registered study protocol and applied consistently.

8. Oocyte Retrieval

Transvaginal ultrasound-guided oocyte retrieval would be performed at the predefined interval after trigger administration. Retrieved oocytes would be assessed for maturity according to standard embryological criteria.

9. Embryological Outcomes

The following would be recorded:

1. total oocytes retrieved;
2. mature MII oocytes;
3. normally fertilized oocytes;

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4. cleavage-stage or blastocyst development;
5. number of transferable embryos;
6. embryo quality.

10. Pregnancy Outcomes

Pregnancy would be assessed using serum β-hCG followed by ultrasonographic confirmation. Outcomes would include biochemical pregnancy, clinical pregnancy, ongoing pregnancy and live birth.

11. Safety Outcome

The principal safety outcome would be moderate-to-severe OHSS, classified according to accepted clinical criteria. Other adverse events would also be documented.

IV. PROPOSED DATA-COLLECTION TABLE

Table 1. Baseline Characteristics of Participants

Variable	GnRH Agonist Group (n=60)*	hCG Group (n=60)*
Age (years)	31.8 ± 3.7	32.1 ± 3.9
BMI (kg/m²)	24.1 ± 3.2	24.4 ± 3.1
Duration of infertility (years)	4.1 ± 2.0	4.3 ± 2.1
AMH (ng/mL)	3.8 ± 1.5	3.7 ± 1.4
Antral follicle count	18.2 ± 5.4	17.9 ± 5.2
Basal FSH (IU/L)	6.7 ± 1.5	6.8 ± 1.6
Previous IVF cycles	1.2 ± 0.8	1.3 ± 0.9

Illustrative values for demonstrating the proposed analysis format; not observed patient data.

V. PROPOSED PRIMARY OUTCOME TABLE

Table 2. Oocyte and Embryological Outcomes

Outcome	GnRH Agonist (n=60)*	hCG (n=60)*	p-value*
Oocytes retrieved	14.2 ± 4.8	14.7 ± 5.0	0.58
Mature MII oocytes	11.7 ± 4.2	12.1 ± 4.3	0.61
Maturation rate (%)	82.4 ± 8.1	82.9 ± 7.8	0.74
Fertilized oocytes	8.9 ± 3.5	9.2 ± 3.6	0.65
Good-quality embryos	4.8 ± 2.1	4.9 ± 2.2	0.81
Blastocysts formed	3.2 ± 1.5	3.3 ± 1.6	0.72

Illustrative values only; p-values are hypothetical and must not be interpreted as actual trial findings.

VI. PROPOSED CLINICAL OUTCOME TABLE

Table 3. Pregnancy and Safety Outcomes

Outcome	GnRH Agonist (n=60)*	hCG (n=60)*
Biochemical pregnancy	25 (41.7%)	29 (48.3%)
Clinical pregnancy	22 (36.7%)	27 (45.0%)
Ongoing pregnancy	20 (33.3%)	25 (41.7%)
Live birth	18 (30.0%)	23 (38.3%)
Moderate/severe OHSS	1 (1.7%)	6 (10.0%)
Cycle cancellation	2 (3.3%)	1 (1.7%)

Illustrative dataset only. These figures are not claimed as actual results.

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VII. STATISTICAL ANALYSIS

Data would be analysed using SPSS, R or an equivalent statistical package. Continuous variables would be expressed as mean ± standard deviation when normally distributed and median with interquartile range when non-normally distributed. Categorical variables would be presented as frequencies and percentages.

An independent-samples t-test would be used for normally distributed continuous outcomes, while the Mann–Whitney U test would be used for non-normal variables. Chi-square or Fisher's exact test would be used for categorical outcomes. Relative risks and 95% confidence intervals would be calculated for pregnancy and OHSS outcomes. A multivariable logistic regression could be conducted to adjust for clinically relevant baseline factors. Statistical significance would be set at $p < 0.05$.

VIII. RESULTS: EXPECTED INTERPRETATION

The proposed analysis is expected to demonstrate broadly comparable oocyte-retrieval and maturation outcomes between the two trigger strategies, while potentially showing a substantially lower OHSS rate with GnRH agonist triggering. This expectation is consistent with randomized evidence demonstrating strong protection against moderate-to-severe OHSS with GnRH agonist triggers.

However, pregnancy outcomes require careful interpretation. GnRH agonist-only triggering can result in luteal-phase insufficiency in fresh autologous cycles. Earlier randomized evidence reported lower live-birth and ongoing-pregnancy outcomes compared with hCG.

More recent evidence also suggests that combined GnRH agonist plus low-dose hCG, commonly called a dual trigger, may improve reproductive outcomes compared with hCG alone in selected GnRH-antagonist cycles. A 2021 meta-analysis of randomized trials involving 1,048 participants reported a higher live-birth rate with dual triggering than with hCG alone.

IX. DISCUSSION

The findings of a randomized comparison should be interpreted in the context of the physiological differences between the two triggers. hCG has a relatively prolonged biological effect and provides sustained luteotropic stimulation. This characteristic makes it effective for supporting the luteal phase but also contributes to the pathophysiology of OHSS. GnRH agonist triggering, in contrast, induces an endogenous gonadotropin surge that is shorter in duration. The resulting reduction in ovarian stimulation after triggering explains its major safety advantage.

The principal clinical concern with GnRH agonist-only triggering is luteal-phase dysfunction. In fresh embryo-transfer cycles, rapid luteolysis and inadequate endogenous luteal support can compromise implantation and pregnancy maintenance. This explains why randomized evidence has historically shown lower pregnancy and live-birth rates with GnRH agonist-only triggering despite its favorable OHSS profile.

Current clinical recommendations therefore emphasize adequate luteal support when GnRH agonist triggering is followed by fresh embryo transfer.

The clinical context is also important. For patients at high risk of OHSS, GnRH agonist triggering is particularly attractive. For patients undergoing freeze-all strategies, the concern regarding fresh-cycle luteal support is less important because embryo transfer is deferred. In selected patients requiring fresh transfer, modified luteal support or a dual-trigger strategy may be considered.

Randomized meta-analytic evidence concerning dual triggering is encouraging. A 2017 meta-analysis involving four RCTs and 527 women found no significant differences in the number of retrieved or mature oocytes but reported improved pregnancy outcomes with dual triggering compared with hCG alone. A later meta-analysis involving 1,048 participants similarly reported a higher live-birth rate with dual triggering.

Thus, the modern evidence base does not support viewing GnRH agonist and hCG simply as interchangeable drugs. Rather, the choice should be individualized according to ovarian response, OHSS risk, embryo-transfer plan and luteal-support strategy.

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The proposed study has several potential limitations. A relatively small sample may limit statistical power for uncommon outcomes such as severe OHSS and live birth. Blinding participants and clinical staff may be difficult because the trigger medications differ. Pregnancy outcomes may also be influenced by embryo quality, maternal age, ovarian reserve and transfer strategy. Furthermore, results from one fertility centre may not be generalizable to all IVF populations.

X. CONCLUSION

Randomized evidence indicates that GnRH agonist triggering has a major safety advantage over hCG with respect to prevention of moderate-to-severe OHSS, but GnRH agonist-only triggering can compromise pregnancy and live-birth outcomes in fresh autologous cycles if luteal support is inadequate. hCG remains an effective trigger but carries greater OHSS risk. Current evidence therefore supports individualized trigger selection rather than a universal preference for one agent. In patients at high risk of OHSS, GnRH agonist triggering is strongly supported, while adequate luteal support is essential when fresh transfer is undertaken. Dual-trigger approaches may offer another strategy for selected patients, although additional high-quality randomized evidence remains valuable.

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