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Efficacy and Reproductive Outcomes of Combined Versus Single Trigger Protocols in Assisted Reproductive Technology: A Meta-Analytical Study

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ABSTRACT: Ovulation triggering is a critical component of assisted reproductive technology (ART), as the final maturation of retrieved oocytes directly influences subsequent fertilization, embryo development, implantation, and reproductive outcomes. Conventional single-trigger protocols using human chorionic gonadotropin (hCG) have been widely applied, whereas combined or dual-trigger approaches incorporating a gonadotropin-releasing hormone (GnRH) agonist with hCG have been investigated as a strategy to reproduce more closely the physiological hormonal events associated with final follicular maturation. This study synthesizes the evidence provided in six studies examining dual versus single ovulation-trigger approaches in in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), with particular attention to reproductive outcomes, ovarian response, live birth, and outcomes in women with diminished ovarian reserve or low response. The methodological approach is based on structured comparative synthesis of the supplied systematic reviews, meta-analyses, retrospective cohort evidence, and comparative clinical studies. The literature generally indicates that dual-trigger protocols may provide clinically meaningful advantages for selected patient populations, although the magnitude and consistency of benefit vary according to ovarian reserve, responder status, treatment characteristics, and outcome definitions. Evidence concerning live birth is particularly important because improvements in intermediate outcomes do not necessarily translate into superior cumulative reproductive success. The analysis highlights the potential value of individualized trigger selection while emphasizing heterogeneity, retrospective evidence, and limitations in direct comparability among studies.

KEYWORDS: Assisted Reproductive Technology, IVF, ICSI, Dual Trigger, Single Trigger, GnRH Agonist, hCG, Ovulation Trigger, Reproductive Outcomes, Meta-Analysis.

1. Introduction

Controlled ovarian stimulation and final oocyte maturation represent fundamental stages of IVF and ICSI treatment. The final ovulation-trigger decision determines the timing and endocrine environment of oocyte maturation before retrieval and consequently has potential implications for the quality and developmental competence of retrieved oocytes. In conventional practice, hCG has served as a principal trigger because of its ability to provide sustained luteinizing hormone-like activity. However, the prolonged biological activity of hCG differs from the physiological pattern associated with an endogenous luteinizing hormone surge.

The dual-trigger strategy was developed to combine the endocrine characteristics of a GnRH agonist-induced endogenous gonadotropin surge with the luteotropic support associated with hCG. In practical terms, this approach seeks to stimulate both luteinizing hormone and follicle-stimulating hormone activity through the GnRH agonist while retaining hCG-mediated support. The underlying rationale is that final follicular maturation may depend not simply on exposure to a single hormonal stimulus but on coordinated endocrine signaling. The comparative evidence synthesized by Zhang et al. specifically examines IVF/ICSI outcomes under different trigger methods, demonstrating the importance of trigger selection as a clinically relevant

variable rather than a merely procedural decision (Zhang et al., 2021).

The clinical question is particularly relevant for patients with diminished ovarian reserve and low ovarian response. These populations may have a restricted follicular cohort and consequently provide fewer opportunities for successful embryo selection. Any intervention capable of improving mature-oocyte yield or downstream reproductive outcomes could therefore have disproportionate clinical importance. Lin et al. reported an association between dual triggering and improved live birth outcomes among women with diminished ovarian reserve, providing a patient-specific rationale for examining dual-trigger protocols beyond conventional overall-population comparisons (Lin et al., 2019).

The research problem addressed in this study is therefore whether combined GnRH agonist–hCG triggering offers measurable reproductive advantages over hCG-only triggering and whether these advantages remain consistent across different ART populations. The objective is to critically synthesize the supplied evidence concerning reproductive outcomes, identify areas of agreement and inconsistency, and establish the clinical and methodological implications of selecting combined rather than single-trigger protocols.

The scope is restricted to the six references supplied for this analysis. Particular attention is given to IVF/ICSI cycles, final oocyte maturation, reproductive outcomes, live birth, low responders, and diminished ovarian reserve. The significance of this analysis lies in its attempt to distinguish theoretical physiological advantages from clinically meaningful reproductive benefits.

2. Literature Review

The supplied literature provides evidence from different levels of clinical investigation. Hu et al. conducted a systematic review and meta-analysis of randomized trials comparing GnRH agonist plus hCG dual triggering with hCG triggering for follicular maturation. The inclusion of randomized evidence provides an important methodological foundation because randomization can reduce confounding associated with patient selection and treatment allocation (Hu et al., 2021). Their work positions the dual-trigger question within comparative clinical evidence rather than relying solely on physiological reasoning.

Zhang et al. broadened the comparison by evaluating outcomes of IVF/ICSI under different trigger methods through systematic review and meta-analysis. This evidence is important because IVF and ICSI encompass heterogeneous patient and laboratory characteristics, meaning that trigger-related effects must be interpreted in the context of the complete ART pathway (Zhang et al., 2021). Their work supports the broader proposition that final oocyte maturation strategy can influence measurable treatment outcomes.

The evidence becomes more population-specific in studies focusing on poor or diminished ovarian response. Sloth et al. examined the effect of dual triggering on reproductive outcomes among low responders through a systematic PRISMA review and meta-analysis. This population is clinically significant because low responders have fewer oocytes available for fertilization and embryo development, potentially magnifying the consequences of suboptimal final maturation (Sloth et al., 2022).

Lin et al. similarly focused on women with diminished ovarian reserve and reported improved live birth outcomes associated with dual triggering. The importance of this study extends beyond the direction of its findings because live birth represents a patient-centered endpoint that is more clinically meaningful than isolated laboratory outcomes. An increase in mature oocytes, for example, becomes clinically consequential only if it contributes to embryo formation, implantation, ongoing pregnancy, and ultimately live birth (Lin et al., 2019).

Observational evidence also contributes to the literature. Dong et al. compared dual triggering with hCG alone in IVF/ICSI cycles using a retrospective cohort design incorporating propensity-score matching. Propensity matching attempts to reduce measurable baseline differences between treatment groups, although it cannot eliminate confounding from unmeasured variables (Dong et al., 2022). This study consequently provides useful real-world comparative evidence while requiring more cautious causal interpretation than randomized trials.

Guner et al. examined reproductive outcomes among women undergoing IVF with fresh embryo transfer cycles. Its focus on fresh transfer is relevant because the effect of a trigger strategy may interact with subsequent treatment decisions, embryo availability, and transfer strategy (Guner et al., 2024). Collectively, these studies suggest that the effectiveness of dual triggering cannot necessarily be represented by a single universal effect across all ART patients.

A central gap emerging from the supplied literature is therefore the difficulty of determining whether observed advantages are intrinsic to dual triggering or concentrated in particular clinical subgroups. Differences in ovarian reserve, response status, cycle characteristics, embryo-transfer practices, and study design can affect observed outcomes. The literature consequently supports a precision-oriented interpretation: dual triggering may

be advantageous under selected circumstances, but universal substitution of hCG with a combined strategy cannot be established solely from the available evidence.

3. Methodology

3.1 Research Design

This study adopts a structured evidence-synthesis and comparative meta-analytical framework based exclusively on the six references supplied. Because the objective is to evaluate the efficacy and reproductive implications of combined versus single triggering, the methodological structure emphasizes comparison between dual-trigger protocols involving GnRH agonist plus hCG and single-trigger protocols based on hCG.

The evidence base includes systematic reviews, meta-analyses, randomized-trial synthesis, retrospective cohort evidence, and population-specific comparative studies. These designs are treated according to their evidentiary characteristics rather than assumed to have equivalent methodological strength.

3.2 Comparative Intervention Model

The principal intervention is the combined or dual-trigger approach, conceptually represented as:

GnRH agonist + hCG → final oocyte maturation → oocyte retrieval → fertilization/ICSI → embryo development → transfer → reproductive outcome

The comparator is:

hCG alone → final oocyte maturation → oocyte retrieval → fertilization/ICSI → embryo development → transfer → reproductive outcome

The analytical distinction is important because the dual trigger is not simply an increased dose of the same intervention. It represents a different endocrine strategy intended to provide complementary hormonal stimulation.

3.3 Outcome Framework

The synthesis prioritizes outcomes along a clinically progressive pathway. Initial outcomes concern follicular and oocyte maturation, followed by fertilization and embryo-related outcomes and finally clinical reproductive endpoints. Live birth receives particular emphasis because it provides a stronger measure of ultimate treatment effectiveness than intermediate laboratory endpoints.

This distinction is especially relevant when interpreting the findings of Lin et al., whose study linked dual triggering with live birth outcomes among women with diminished ovarian reserve (Lin et al., 2019). A theoretically favorable trigger protocol should therefore be considered clinically valuable only when improvements extend sufficiently downstream to affect meaningful reproductive outcomes.

3.4 Evidence Integration

Evidence was interpreted according to study population, intervention, comparator, outcomes, and methodological design. Systematic reviews and meta-analyses were used as high-level evidence for identifying overall patterns, while individual cohort and population-specific studies were used to examine clinical context.

The methodological framework also recognizes potential heterogeneity. Differences in patient selection, ovarian response, treatment protocols, embryo-transfer conditions, and study design may produce apparently inconsistent findings without necessarily representing genuine contradictions. Thus, rather than treating every study result as directly interchangeable, this analysis evaluates whether observed effects are broadly consistent or conditional upon specific clinical circumstances.

3.5 Analytical Model

The conceptual analytical model can be expressed as:

Trigger strategy → final oocyte maturation → mature oocyte availability → embryo-development potential → implantation/pregnancy → live birth

Patient characteristics such as ovarian reserve and responder status may act as effect-modifying factors. In this model, the same trigger strategy may produce different outcomes in normal responders compared with low responders or women with diminished ovarian reserve.

This framework is consistent with the literature's population-specific emphasis. Sloth et al. investigated low responders, while Lin et al. concentrated on diminished ovarian reserve, indicating that treatment effects should not automatically be generalized across the entire ART population (Sloth et al., 2022; Lin et al., 2019).

4. Results / Findings

The synthesized evidence indicates an overall research trend favoring the clinical investigation of dual-trigger protocols, although the strength and consistency of the apparent benefit vary across populations and endpoints. The systematic reviews and meta-analyses supplied by Hu et al., Sloth et al., and Zhang et al. collectively establish that dual versus single triggering is a clinically substantive comparison rather than a purely theoretical intervention question (Hu et al., 2021; Sloth et al., 2022; Zhang et al., 2021).

One important pattern concerns final follicular and oocyte maturation. The rationale for combining GnRH agonist and hCG is based on providing complementary

endocrine stimulation. Consequently, potential improvements in mature-oocyte availability represent one of the principal mechanisms through which dual triggering could influence downstream ART outcomes. However, maturation outcomes alone cannot establish superiority in terms of patient-centered reproductive success.

The evidence becomes particularly relevant among low responders and women with diminished ovarian reserve. Sloth et al. specifically evaluated low responders and identified the need to assess dual-trigger effectiveness within this restricted ovarian-response population rather than assuming that findings from broader IVF populations apply equally to them (Sloth et al., 2022). This population-specific perspective is supported by Lin et al., whose investigation of women with diminished ovarian reserve reported improved live birth outcomes associated with dual triggering (Lin et al., 2019). The finding is clinically significant because live birth represents a substantially more meaningful endpoint than oocyte yield alone.

The retrospective cohort analysis by Dong et al. adds real-world evidence by comparing dual triggering with hCG alone in IVF/ICSI cycles using propensity-score matching (Dong et al., 2022). Such an approach strengthens comparability between observational groups but does not provide the same protection against unmeasured confounding as randomization. Guner et al. further contributes evidence from fresh embryo-transfer cycles, reinforcing the importance of interpreting trigger efficacy within specific treatment pathways rather than as an isolated intervention (Guner et al., 2024).

The evidence also indicates that superiority cannot be considered uniform across every outcome. A trigger protocol may improve a proximal endpoint without producing a proportional improvement in live birth. Therefore, the clinically relevant result is not merely whether dual triggering modifies maturation but whether the effect persists across the complete reproductive pathway.

Overall, the findings support dual triggering as a potentially valuable strategy, particularly for selected patients with diminished ovarian reserve or low response. Nevertheless, the evidence does not justify interpreting the combined protocol as universally superior to hCG alone. Variation in study populations, methodological designs, and reproductive endpoints remains an important source of uncertainty.

5. Discussion

The principal implication of the synthesized evidence is that trigger selection should be interpreted as a component of individualized ART management rather than a universally interchangeable procedural step. The physiological rationale for dual triggering is persuasive because it combines two hormonal mechanisms associated with final follicular maturation. Nevertheless, physiological plausibility must be distinguished from demonstrated clinical benefit.

The strongest clinical argument for dual triggering arises when the patient has limited ovarian reserve or reduced ovarian response. In such patients, every mature oocyte may carry greater potential value because the number of available oocytes is already constrained. The evidence reported by Lin et al. is therefore particularly important: the association between dual triggering and improved live birth outcomes in women with diminished ovarian reserve indicates that the potential benefit may extend beyond laboratory endpoints (Lin et al., 2019).

At the same time, the results should not be interpreted as evidence that all patients will obtain the same benefit. Sloth et al.'s concentration on low responders demonstrates the importance of population stratification (Sloth et al., 2022). If treatment effects are modified by ovarian reserve or responder status, then an aggregate estimate across heterogeneous populations could obscure clinically important subgroup differences.

Another important consideration is methodological heterogeneity. Hu et al.'s systematic review and meta-analysis of randomized trials provides evidence generated under stronger control of confounding, whereas Dong et al. and Guner et al. provide observational clinical evidence (Hu et al., 2021; Dong et al., 2022; Guner et al., 2024). Retrospective evidence can capture real-world treatment patterns, but treatment allocation may itself reflect clinicians' assessment of patient prognosis. Consequently, an observed association between dual triggering and reproductive success may partly reflect characteristics of the patients selected for the intervention.

The literature also highlights a distinction between intermediate and ultimate outcomes. Increased maturation or favorable laboratory parameters may be clinically useful, but patients ultimately seek pregnancy and live birth. Lin et al.'s emphasis on live birth is consequently valuable for interpreting whether the proposed biological advantages of dual triggering translate into meaningful reproductive outcomes (Lin et al., 2019).

From a practical perspective, the evidence supports a selective rather than indiscriminate implementation strategy. Clinicians may consider dual triggering particularly relevant when diminished ovarian reserve, low response, or concerns regarding final oocyte maturation are present. However, the decision should remain integrated with the overall stimulation protocol and individual clinical characteristics.

The major limitation of the evidence synthesis is the relatively small and heterogeneous supplied evidence base. The studies differ in design, population, treatment context, and outcome emphasis. Observational studies also retain potential residual confounding despite statistical adjustment. Furthermore, differences between IVF and ICSI populations may affect the interpretation of downstream reproductive outcomes. These limitations restrict the extent to which a single generalized estimate of treatment superiority can be inferred.

6. Conclusion

The comparative evidence reviewed in this study indicates that combined GnRH agonist–hCG triggering represents a clinically important alternative to conventional hCG-only triggering in ART. Its theoretical advantage arises from the complementary endocrine stimulation associated with dual triggering, while clinical evidence suggests that potential reproductive benefits may be particularly relevant among women with diminished ovarian reserve and low ovarian response.

The evidence synthesized from systematic reviews, meta-analyses, and comparative clinical studies supports continued consideration of dual triggering, but it does not establish universal superiority across all IVF/ICSI patients and all reproductive endpoints. The strongest interpretation is therefore one of patient-specific effectiveness rather than blanket replacement of single-trigger protocols.

Future research should prioritize adequately powered randomized comparisons, consistent definitions of ovarian response and reproductive outcomes, and subgroup analyses based on ovarian reserve and patient characteristics. Particular emphasis should be placed on cumulative live birth rather than isolated laboratory endpoints. Such research would help determine whether the apparent advantages of dual triggering reflect a broadly applicable treatment effect or a clinically targeted benefit for specific ART populations.

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