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Review Article Volume 2 | Issue 1

KOS Journal of Public Health and Integrated Medicine
https://kelvinpublishers.com/journals/public-health-and-integrated-medicine.php

Critical Review of the Literature: Ovarian Stimulation and Oocyte Maturation Triggering Protocols for In Vitro Fertilization (IVF)

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Received: April 22, 2026 **Accepted:** May 04, 2025; **Published:** May 06, 2025

Citation: Alejandro Gonzalez. (2026) Critical Review of the Literature: Ovarian Stimulation and Oocyte Maturation Triggering Protocols for In Vitro Fertilization (IVF). *KOS J Pub Health Int Med.* 2(1): 1-6.

1. Introduction

Ovarian stimulation protocols are the cornerstone of In Vitro Fertilization (IVF) treatment, having evolved significantly since its inception. Historically, conventional approaches were designed with the aim of maximizing the number of oocytes retrieved, under the paradigm that "more is better". However, in the last decade there has been a shift towards gentle stimulation protocols, which prioritize safety, reduced treatment burden, and the overall patient experience. This development has led to a central controversy in reproductive medicine about the clinical efficacy of gentle stimulation compared to conventional high-dose regimens. Simultaneously, another critical aspect of the IVF cycle that remains the subject of debate is the choice of agent for the triggering of final oocyte maturation. While human chorionic gonadotropin (HCG) has long been the gold standard, the use of a gonadotropin-releasing hormone (GnRH) agonist has been proposed as an alternative, especially in protocols with GnRH antagonists. The aim of this review is to synthesize and critically evaluate the evidence from recent meta-analyses on these two fundamental aspects of IVF treatment: the intensity of ovarian stimulation and the selection of the triggering agent, in order to offer a clear perspective on the current state of evidence-based practice.

2. Methodological Evaluation of Baseline Reviews

The validity of any literature review depends fundamentally on the methodological quality of the studies that compose it. Before analyzing clinical findings, it is imperative to critically evaluate the design, inclusion criteria, study populations, and outcomes measured in systematic reviews and baseline meta-analyses. This evaluation determines the robustness of its conclusions and their applicability in daily clinical practice. The methodological components of the two meta-analyses that form the basis of this review are broken down below.

2.1. Meta-analysis analysis on gentle vs. conventional stimulation [1]

The meta-analysis by Datta et al. [1] provides a comprehensive and up-to-date assessment of gentle ovarian stimulation. Its key methodological components include:

***Study objective:** To evaluate parallel-group randomized controlled trials (RCTs) comparing the clinical outcomes and cost-effectiveness of gentle versus conventional ovarian stimulation.

***Inclusion criteria:** The operational definition of "gentle stimulation" (MD-IVF) was rigorous, including only studies that used a daily gonadotropin dose of ≤150 IU, either alone or in combination with oral compounds.

***Populations analyzed:** The authors segmented the RCTs included into three clinically relevant patient groups to allow

for nuanced analysis: poor responders, normal responders, and hyperresponder non-PCOS.

***Primary and secondary outcomes:** The primary outcomes assessed were Live Birth Rate (WHR) by randomization, incidence of Ovarian Hyperstimulation Syndrome (OHSS), and Cycle Cancellation Rate (CRC). Secondary outcomes included Cumulative Live Birth Rate (CLBR), Ongoing Pregnancy Rate (OPR), total gonadotropin dose, and cost of treatment.

***Quality assessment:** The authors performed a rigorous assessment of risk of bias for each included study using the Cochrane Handbook and assessed the overall quality of the evidence (QoE) for each outcome using the GRADE system.

2.2. Meta-analysis of GnRH agonist triggering vs. HCG [2]

The meta-analysis by Griesinger et al. [2] was a pioneering work that sought to consolidate the evidence on an alternative to standard HCG triggering. Its methodological characteristics were:

***Study Objective:** To systematically collect and evaluate the available evidence on the clinical efficacy of triggering with GnRH agonists in IVF cycles using a protocol with GnRH antagonists.

***Inclusion Criteria:** Very strict inclusion criteria were applied. Of 23 publications identified, only 3 met the requirements: prospective RCT design, use of a randomized control group to receive HCG for final oocyte maturation, and luteal phase support without HCG.

***Population Analyzed:** Participants in the included studies were normovulatory women undergoing IVF treatment.

***Outcomes Assessed:** Multiple outcomes were analyzed, including clinical pregnancy per randomized patient, number of oocytes retrieved, proportion of mature oocytes (metaphase II), fertilization rate, embryo quality score, first trimester miscarriage rate, and incidence of OHSS.

With a clear understanding of the methodological basis of these fundamental reviews, the following section will proceed to synthesize their key clinical findings.

3. Synthesis of Findings: Mild Ovarian Stimulation vs. Mild Ovarian Stimulation Conventional

The comparison between gentle and conventional ovarian stimulation protocols is critical in modern IVF, as it directly addresses the balance between efficacy (achieving pregnancy), safety (minimizing complications such as OHSS), and efficiency (reducing the burden of treatment and cost to the patient). This section systematically breaks down the findings of the meta-analysis by Datta et al. [1], which provides the most comprehensive and recent evidence on this topic, across the different clinical and laboratory results.

3.1. Clinical efficacy in different patient populations

The main concern with gentle stimulation protocols has been their potential to compromise success rates. However, the meta-analysis by [1] provides robust evidence that refutes the hypothesis that gentle stimulation protocols compromise success rates.

***Live Birth Rate (LBR) by Randomization:** The meta-analysis found no statistically significant differences in LBR between gentle (MD-IVF) and conventional (CD-IVF) stimulation in either patient group. Relative risks (RRs) were 0.91 for poor responders, 0.88 for normal responders, and 0.98 for hyperresponders. The quality of the evidence for this crucial outcome was rated as moderate.

***Cumulative Live Birth Rate (CLBR):** When analyzing the 5 RCTs that reported on the outcomes of subsequent fresh and frozen cycles, CLBRs were also similar between the two approaches (RR 0.96). This finding, which reflects the overall success of a single oocyte retrieval cycle, was also supported by moderate quality of evidence.

***Clinical Pregnancy Rate (CPR) and Ongoing Pregnancy Rate (OPR):** Consistently, analyses for clinical pregnancy rate and ongoing pregnancy rate showed no significant differences between stimulation protocols in any of the patient subgroups.

3.2. Safety profile and cycle efficiency

Beyond efficacy, patient safety and cycle efficiency are paramount considerations that distinguish gentle protocols.

***Incidence of Ovarian Hyperstimulation Syndrome (OHSS):** This is one of the strongest findings of the meta-analysis. The risk of developing OHSS was significantly lower with MD-IVF in both normal responders (RR 0.22) and hyperresponders (RR 0.47). The quality of the evidence for this safety outcome was moderate.

***Cycle Cancellation Rate (CCR):** The findings on cycle cancellation were more nuanced. Rates were comparable in poor responders and hyperresponders. However, CRC was significantly increased with MD-IVF in the normal responder group (RR 2.08), although this finding is based on very low-quality evidence, probably due to heterogeneity in cancellation criteria between studies.

3.3. Laboratory results and cost-effectiveness

The stimulation strategy also has direct implications in the laboratory and in the economic burden for patients.

***Oocyte and Embryo Yield and Quality:** As expected, with MD-IVF protocols fewer oocytes were retrieved and, consequently, fewer embryos were created. However, a key finding was that the proportion of high-quality embryos was similar between the MD-IVF and CD-IVF groups in the three population types.

***Gonadotropin Dosage and Cost:** Consistently across all studies, MD-IVF was associated with significantly lower gonadotropin use and, as a direct result, lower overall cost of treatment.

While these findings redefine the approach to stimulation, the success of the cycle is equally dependent on the final oocyte maturation strategy, an area with its own critical controversies.

4. Synthesis of Findings: GnRH Agonist vs. HCG Triggering

The agent used to trigger final oocyte maturation is a critical step in the IVF cycle. This decision influences not only the maturation and quality of the retrieved oocytes, but also the hormonal environment of the luteal phase, which has a potential impact on both patient safety (OHSS risk) and cycle success. This section will focus on the findings of the meta-analysis by Griesinger et al. [2] to assess the efficacy and consequences of using a GnRH agonist as an alternative to traditional HCG.

4.1. Benchmarking triggering protocols

The meta-analysis by Griesinger et al. [2] directly compared the results of GnRH agonist triggering versus the HCG standard in normovulatory women using a GnRH antagonist protocol. The key findings are summarised in the table below:

Evaluated Parameter GnRH Agonist vs. HCG Triggering (Findings [2])

Lab Results No significant differences were found in the number of oocytes retrieved, the proportion of oocytes in metaphase II, the fertilization rate or the embryo quality score.

Probability of Clinical Pregnancy It was associated with a significantly reduced probability of achieving a clinical pregnancy (OR 0.21, P = 0.03).

First Trimester Pregnancy Loss The odds of pregnancy loss increased, although the outcome was marginally significant (P = 0.05) and the confidence interval crossed the unit.

Incidence of OHSS The available data were insufficient to draw conclusions about the incidence of OHSS.

In summary, the findings of this meta-analysis identified a clear compromise: although GnRH agonist triggering is as effective as HCG in achieving oocyte maturation and fertilization at the laboratory level, it was associated with worse pregnancy outcomes in the studies analyzed at that time.

5. Discussion and Critical Synthesis

A comprehensive review requires the integration of disparate findings into a cohesive narrative that informs clinical practice. This discussion section will integrate findings on the intensity of ovarian stimulation and the choice of triggering agent to build a unified understanding of current trends. It is crucial to recognize that the evolution of both fields is intrinsically linked to the widespread adoption of protocols with GnRH antagonists. Not only did this innovation provide the flexibility needed to implement gentler, late-onset pacing protocols, but it was also the essential prerequisite that made GnRH agonist triggering a viable and safer option.

5.1. Re-evaluation of the “more is better” paradigm

The findings of Datta et al. [1] present a direct challenge to the traditional paradigm of “more is better” in ovarian stimulation. Accumulating evidence of similar live birth rates, both by cycle started and cumulative, suggests that aggressive seeking for a higher number of oocytes through higher gonadotropin doses does not necessarily translate into an increased likelihood of having a baby. When this fact is combined with the clear benefits of gentle stimulation—a significantly lower risk of OHSS and lower treatment costs—the argument for a more moderate approach becomes compelling. This evidence supports a shift towards a more patient-centred practice, where safety and reducing the burden of treatment are prioritised without compromising the end goal.

5.2. The triggering dilemma: efficacy vs. effectiveness security

On the other hand, the meta-analysis by Griesinger et al. [2] illustrates a classic clinical dilemma. GnRH agonist triggering has been considered a promising strategy to almost completely eliminate the risk of OHSS (a safety benefit that could not be concluded in this meta-analysis but is widely recognized in current clinical practice). However, the data analysed in this pioneering review showed a significant penalty in clinical pregnancy rates. This creates a conflict for the clinician: opting for a potentially safer strategy that, based on the evidence at the time, could reduce the patient's chances of success in that fresh transfer cycle. This commitment underscores the importance of the clinical context and the need for additional strategies, such as embryo cryopreservation, to mitigate luteal phase deficiencies associated with this type of triggering.

5.3. Limitations of current evidence

It is critical to recognize the inherent limitations of the evidence presented in order to properly contextualize the conclusions:

***Clinical Heterogeneity:** Both meta-analyses, especially that of [1], had to pool studies with significant variations in treatment protocols, definitions of patient populations (e.g., "poor responder"), and cycle cancellation criteria. This heterogeneity reduces the quality of the evidence for certain outcomes and may mask effects in specific subgroups.

***Quality of the Evidence (QoE):** For several important outcomes, the quality of the evidence was rated as low or very low. For example, in the analysis by [1], the cycle cancellation rate and embryo quality results were based on low-quality evidence, limiting the firmness of conclusions in those areas.

***Age of Data:** The meta-analysis on triggering [2] is based on RCT data from nearly two decades ago. Since then, clinical practices, and in particular luteal phase support protocols after GnRH agonist triggering, have evolved considerably. Therefore, the applicability of its findings on pregnancy rates to current practice should be viewed with caution.

These limitations do not invalidate the findings, but rather underscore the need for clear clinical guidelines that take into account these uncertainties and for well-designed future research.

6. Implications for Clinical Practice and Future Research

A critical review of the literature should not only summarize past evidence, but also serve as a guide for present clinical practice and guide future lines of research. This final section aims to translate the synthesized findings into tangible recommendations for reproductive health professionals and identify the most critical knowledge gaps that need to be addressed in order to further optimize IVF treatments.

6.1. Recommendations for clinical practice

6.1.1. Consider Gentle Stimulation as First-Line: Given the strong evidence of comparable efficacy in live birth rate (both cycle and cumulative) and a superior safety profile (lower risk of OHSS and lower cost), gentle ovarian stimulation (defined as ≤150 IU/day gonadotropin) should be considered a viable first-line strategy for all categories of responders: poor, normal and hyper-responders. The decision to use higher doses should be based on specific clinical indications rather than being the default approach.

6.1.2. Strategic Use of GnRH Agonist Triggering: In light of the lower clinical pregnancy rates reported in the [2]. meta-analysis for fresh transfers, HCG triggering remains the gold standard for most cycles. However, triggering with GnRH agonist is an invaluable option and should be considered in patients at elevated risk of OHSS. In these cases, its use should preferably be accompanied by a "freeze-all" strategy to transfer the embryos into a subsequent cycle with an optimized endometrial environment, an approach that was not evaluated in the 2006 meta-analysis but has become standard practice.

6.2. Directions for Future Research

6.2.1. Standardization of Protocols and Outcomes: There is a compelling need for future RCTs to use standardized definitions for patient populations (e.g., Bologna criteria for poor responders) and "soft" pacing protocols. This will minimise the clinical heterogeneity that has limited the quality of the evidence in previous meta-analyses and allow for more robust conclusions.

6.2.2. Update of the Evidence on Triggering: A new systematic review and meta-analysis evaluating GnRH agonist triggering is urgently needed. Such a review should incorporate the numerous RCT data from the last decade, including modern and optimized luteal phase support protocols and comparison of outcomes in fresh versus freeze transfer cycles of all embryos.

6.2.3. Focus on Cumulative Outcomes: The Cumulative Live Birth Rate per oocyte retrieval cycle should be adopted as the primary primary outcome in future trials. This indicator better reflects the overall success of the treatment from the patient's perspective, as it considers the potential of all embryos generated in a single stimulation cycle.

7. Conclusion

This critical review of the literature reveals a clear trajectory in IVF practice towards safer, patient-centred strategies. Current evidence strongly supports the use of gentle ovarian stimulation protocols, which offer pregnancy efficacy comparable to conventional high-dose protocols, but with significant benefits in terms of patient safety, by dramatically reducing the risk of OHSS, and efficiency, by decreasing the burden of treatment and costs. While the choice of oocyte ripening trigger agent still presents a trade-off between efficacy in fresh cycles and safety, which requires individualized clinical decision-making, the general trend is unequivocal. Reproductive medicine is moving towards a more nuanced and personalized approach, where the optimization of clinical benefit is achieved not by maximizing a single parameter, but by balancing cumulative efficacy with patient safety and treatment sustainability.

8. References

1. Datta AK, Maheshwari A, Felix N, et al. (2021) Mild versus conventional ovarian stimulation for IVF in poor, normal and hyper-responders: A systematic review and meta-analysis. Human Reproduction Update. 27(2): 229-253.
2. Griesinger G, Diedrich K, Devroey P, (2006) GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis. Human Reproduction Update. 12(2): 159-168.