Kelvin Open Science Publishers
Connect with Research Community

Review Article ***Volume 2 | Issue 1***

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

Technical Analysis: Ovarian Stimulation and Oocyte Maturation Protocols in Assisted Reproduction

Dr. Alejandro Gonzalez

*Corresponding author: Dr Alejandro Gonzalez, USIOP/INEBIR Sevilla, Spain

Received: April 22, 2026 **Accepted:** May 05, 2026; **Published:** May 07, 2026

Citation: Alejandro Gonzalez. (2026) Technical Analysis: Ovarian Stimulation and Oocyte Maturation Protocols in Assisted Reproduction. *KOS J Pub Health Int Med.* 2(1): 1-6.

1. Executive Summary

This paper synthesizes the scientific evidence from two critical meta-analyses published in Human Reproduction Update on the efficacy and safety of various strategies in in vitro fertilization (IVF).

The main findings are divided into two aspects:

1. Mild Ovarian Stimulation (MD-IVF): The use of low-dose gonadotropins (≤150 IU daily) shows no significant difference in live birth rates (LBR)-both per cycle and cumulative-compared to conventional stimulation (CD-IVF), regardless of whether the patient has a low, normal, or high response. However, MD-IVF drastically reduces the risk of Ovarian Hyperstimulation Syndrome (OHSS) and decreases treatment costs.

2. Maturation Trigger with GnRH Agonists (GnRHa): In protocols with GnRH antagonists, the use of an agonist for the final trigger of oocyte maturation produces a quantity and quality of oocytes and embryos similar to that obtained with human chorionic gonadotropin (hCG). However, it is associated with a significantly lower probability of achieving a clinical pregnancy and a tendency to greater gestational losses in the first trimester.

2. Mild Ovarian Stimulation (MD-IVF) vs. Conventional (CD-IVF)

Mild stimulation is defined as a protocol that uses ≤150 IU daily of gonadotropins, with the aim of limiting the number of oocytes and reducing the stress and cost of treatment.

Clinical Results and Efficacy

Analysis of 31 randomised controlled trials (RCTs) demonstrates that MD-IVF is a viable alternative for all categories of patients:

***Live Newborn Rates (LBR):** There are no significant differences in LBRs by randomization between MD-IVF and CD-IVF in either response group:

***Responders:** Relative Risk (RR) 0.91 (CI 0.68, 1.22).
***Normal responders:** RR 0.88 (CI 0.69, 1.12).
***Hyperresponders (non-PCOS):** RR 0.98 (CI 0.79, 1.22).

***Cumulative LBR:** Data from 5 RCTs (n = 2037) confirm that the cumulative rate is similar in the three types of patients (RR 0.96; CI 0.86, 1.07), supporting the use of MD-IVF as first-line treatment.

Laboratory Parameters

Although mild stimulation prioritizes quality over quantity, differences in oocyte performance are observed:

***Number of oocytes:** Significantly fewer oocytes are recovered with MD-IVF in patients with poor and normal response.

* **Embryo quality:** Despite producing fewer total embryos,

the proportion of high-quality embryos is similar between low-dose and conventional-dose protocols in all populations analyzed.

Economic and Security Factors

Variable	Impact of MD-IVF	Evidence
OHSS Risk	Significant reduction in normal responders and hyperresponders.	RR 0.22 to 0.47
Cost of Treatment	Significantly lower due to lower gonadotropin use.	Documented at multiple sites
Cancellation Fee	Higher in normal responders, but comparable in poor and hyper-responders.	RR 2.08 in normal

3. GnRH Agonist Shooting in Antagonist Protocols

The use of GnRH agonists to induce LH spike and final oocyte maturation is feasible when using GnRH antagonists to prevent premature ovulation.

Efficacy Comparison: GnRHa vs. hCG

The meta-analysis of the systematic evidence yields the following critical results:

***Clinical Pregnancy:** The use of GnRH agonists is associated with a significant reduction in the likelihood of achieving a clinical pregnancy compared to the standard hCG (P = 0.03; Combined odds ratio of 0.21).

***Gestational loss:** An increase in the odds of pregnancy loss was observed during the first trimester after shooting with GnRHa, although the confidence interval crossed the unit (11.51; CI 0.95–138.98; P = 0.05).

***Oocyte Parameters:** No significant differences were found in:

*Number of oocytes recovered.
*Proportion of oocytes in Metaphase II (MII).
*Fertilization rate.
*Embryo quality score.

Conclusion on the Shot

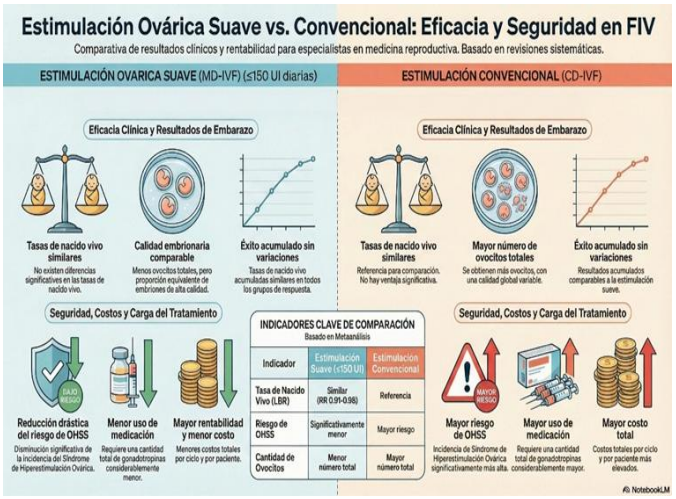
Although GnRHa is effective in obtaining oocytes with fertilization and embryo division capacity comparable to hCG, the final clinical outcome (ongoing pregnancy) is inferior, suggesting a potential negative impact on endometrial receptivity or luteal phase support.

4. Ovarian Hyperstimulation Syndrome (OHSS)

One of the central arguments for the transition to milder protocols is the mitigation of OHSS, a serious complication of ovarian stimulation.

***Low-Dose Efficacy:** In hyperresponder patients, MD-IVF markedly reduced the risk of any grade of OHSS (RR 0.47).

***Data Limitations:** In studies on GnRHa triggering, the incidence of OHSS was null or unreported, which prevents definitive conclusions about its specific advantage in that context from the data analyzed, although the theoretical mechanism suggests a reduction in risk.



5. Final Summary

5.1. Ovarian stimulation protocols

The choice of protocol should be based on markers of ovarian reserve (AMH and RFA) and patient characteristics such as age and BMI.19,24.

Protocol	Indicated Population	Pros	Disadvantages
GnRH antagonist	General population, high responders	Lower risk of **OHSS**, shorter cycle time, allows trigger with agonist.1	Slightly lower number of oocytes compared to the long protocol.1
Agonist de la GnRH (Largo)	Normorespondedoras, endometriosis	Lower premature ovulation rate, better control of follicular growth.3	Higher risk of **OHSS**, higher cost and duration.1
Mild stimulation	Responders or Elective Casualties	Lower cost, lower psychological burden, drastic reduction in **OHSS.12,8**	Lower total number of oocytes (although similar cumulative live birth rate).6

- **Individualization of dose**: The initial dose of **FSH** (typically **150-225 IU/day**) should be adjusted according to **AMH** and **RFA.14 Doses above** 300 IU/day **have not demonstrated clear benefits in low responders and increase costs.30.**
- **Reserve markers**: **AMH** is considered the most reliable predictor of ovarian response, regardless of the patient's age.23,28 An **AMH level < 1.18 ng/ml** or an **RFA ≤ 5** are predictors of low response.24.

Triggering Oocyte Maturation

The goal is to mimic the LH peak to induce final meiosis of the oocyte.

hCG (Recombinant Corifollitropin/hCG): Traditional gold standard. It provides a prolonged stimulus that ensures maturation, but increases the risk of OHSS in high-risk patients.51.

GnRH agonist (GnRHa): Used in antagonist protocols. It induces an endogenous peak of LH and FSH. It is the strategy of choice for total prevention of OHSS, although it requires a "freeze-all" strategy (vitrification of all embryos) or intensive luteal support due to the resulting luteal insufficiency.37,45.

Dual Trigger (GnRHa + hCG): It consists of the simultaneous administration of both drugs.

- It is associated with an increase in the number of mature oocytes (MII), a higher rate of blastocyst formation, and better live birth rates in normal responders and patients with a history of low oocyte maturation.38,40,50
- In low responders, the results are controversial, although some meta-analyses suggest an improvement in the number of oocytes recovered.41,49

Special Population Considerations

Cancer patients: In endometrial or breast cancer, the use of **letrozole** together with gonadotropins is recommended to keep estradiol levels low without compromising oocyte retrieval.15,17

Low Responders (Bologna/POSEIDON Criteria): It is suggested to consider pretreatment with androgens (transdermal or DHEA) or protocols such as **ANDRO-IVF**, although the evidence remains limited and is not routinely recommended by international guidelines.9,1

Luteal Phase Support (LPS): The use of vaginal **progesterone** is the standard. Oral **didrogesterone** is a likely alternative, although some guidelines suggest caution due to the lack of long-term safety data in offspring.2

Security and Surveillance

Risk of OHSS: In patients with >15-18 follicles of ≥11 mm or elevated estradiol levels, the trigger with **GnRH agonist should be performed** and all embryos vitrified! SCH-21.

6. References

1. ESHRE guideline: ovarian stimulation for IVF/ICSI† Revisión Sistemática. Human Reproduction Open·2020·347.
2. Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing in vitro fertilisation plus intracytoplasmic sperm injection (IVF/ICSI). Revisión Sistemática
3. The Cochrane database of systematic reviews·2024·6
4. Evaluation of Ovarian Reserve Tests and Age in the Prediction of Poor Ovarian Response to Controlled Ovarian Stimulation-A Real-World Data Analysis of 89,002 Patients Estudio Observacional. Frontiers in Endocrinology·2021·22.
5. Ovarian Stimulation Protocol in IVF: An Up-to-Date Review of the Literature. Revisión de Literatura
6. Current pharmaceutical biotechnology·2016·79.
7. Mild versus conventional ovarian stimulation for IVF in poor, normal and hyper-responders: a systematic review and meta-analysis Metaanálisis. Human Reproduction Update·2020·54.
8. The case for mild stimulation for IVF: recommendations from The International Society for Mild Approaches in Assisted Reproduction. Revisión de Literatura. Reproductive biomedicine online·2022·7.
9. Ovarian stimulation protocols for IVF: is more better than less? Revisión de Literatura Reproductive biomedicine online·2017·60.
10. Individualization of controlled ovarian stimulation in vitro fertilization using ovarian reserve markers. Revisión de Literatura. Gynecological Minerva·2017·15.
11. Individualization of FSH Doses in Assisted Reproduction: Facts and Fiction. Frontiers in Endocrinology·2019·41
12. Prediction of metaphase II oocytes according to different serum Anti-Müllerian hormone (AMH) levels in antagonist ICSI cycles Estudio Observacional. JBRA Assisted Reproduction·2016·12.
13. The best ovarian reserve marker to predict ovarian response following controlled ovarian hyperstimulation: a systematic review and meta-analysis Metaanálisis. Systematic Reviews·2024·7.
14. hCG Triggering in ART: An Evolutionary Concept. International Journal of Molecular Sciences·2017·21.
15. GnRH agonist versus HCG triggering in different IVF/ICSI cycles of same patients: a retrospective study Estudio Observacional. Journal of Obstetrics and Gynaecology·2019·7.
16. Reproductive Outcome After GnRH Agonist Triggering with Co-Administration of 1500 IU hCG on the Day of Oocyte Retrieval in High Responders: A Long-Term Retrospective Cohort Study Estudio Observacional. Frontiers in Endocrinology·2022·5.
17. GnRH agonist and hCG (dual trigger) versus hCG trigger for final follicular maturation: a double-blinded, randomized controlled study. Ensayo Controlado Aleatorizado. Human reproduction·2020·73.
18. GnRH agonist and hCG (dual trigger) versus hCG trigger for follicular maturation: a systematic review and meta-analysis of randomized trials Metaanálisis. Reproductive Biology and Endocrinology : RB&E·2021·23.
19. Triggering of ovulation for GnRH-antagonist cycles in normal and low ovarian responders undergoing IVF/ICSI: A systematic review and meta-analysis of randomized trials. Metaanálisis. European journal of obstetrics, gynecology, and reproductive biology·2023·8.
20. Final Oocyte Maturation in Assisted Reproduction with Human Chorionic Gonadotropin and Gonadotropin-releasing Hormone agonist (Dual Trigger) Revisión Sistemática. JBRA Assisted Reproduction·2016·28.
21. Dual trigger with gonadotropin-releasing hormone and human chorionic gonadotropin for poor responders Estudio Observacional. Journal of the Turkish German Gynecological Association·2018·11.
22. ESGO/ESHRE/ESGE Guidelines for the fertility-sparing treatment of patients with endometrial carcinoma, Guía Clínica. Human Reproduction Open·
23. ESGO/ESHRE/ESGE Guidelines for the fertility-sparing treatment of patients with endometrial carcinoma Guía Clínica. International Journal of Gynecological Cancer·2023.
24. ANDRO-IVF: a novel protocol for poor responders to IVF controlled ovarian stimulation Ensayo No Aleatorizado. JBRA Assisted Reproduction·2018·11.
25. Questionable recommendation for LPS for IVF/ICSI in ESHRE guideline 2019: ovarian stimulation for IVF/ICSI Reporte de Caso.