The Effect of Double Stimulation Protocol (DuoStim) in Poor Ovarian Responders: A Systematic Review and Meta-Analysis

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Abstract

Background: Managing low ovarian response remains challenging despite advancements in assisted reproductive technology (ART). Although several approaches have been proposed, there is no strong evidence that a particular stimulation protocol is superior over the other in terms of improving reproductive outcomes in this group of women. The double stimulation protocol (DuoStim) suggests ovarian stimulation during both the follicular phase and the luteal phase of the same ovarian cycle; hence, facilitating two oocyte retrievals in the shortest amount of time.
Objective: This study assessed the effect of the double stimulation protocol (DuoStim) on poor ovarian responders in terms of cumulative live birth rates and clinical pregnancy rates, and compared these outcomes to conventional stimulation protocols.
Methods: This is a systematic review and meta-analysis of randomized controlled trials (RCT), cohort and cross-sectional studies in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. Data from eligible journals were tabulated and analyzed using Cochran's Q and I^2 tests.
Results: Eight studies involving poor ovarian responders were included in the meta-analysis. Pooled analysis demonstrated no significant difference between DuoStim and conventional ovarian stimulation protocols in clinical pregnancy rate (OR 0.99, 95% CI 0.75–1.30) and cumulative live birth rate (OR 0.87, 95% CI 0.59–1.28). Fertilization rates were likewise comparable between groups. Nevertheless, several included studies reported higher oocyte yield and greater numbers of mature oocytes and blastocysts with DuoStim
Conclusion: Current evidence does not demonstrate significant superiority of DuoStim over conventional ovarian stimulation protocols in terms of clinical pregnancy rates, cumulative live birth rates, or fertilization rates among poor ovarian responders. However, DuoStim appears to be an effective strategy for increasing oocyte yield within a shorter treatment timeframe. Its use may be particularly relevant in selected patients with diminished ovarian reserve, advanced maternal age, or urgent fertility preservation needs. Further high-quality prospective trials are warranted to clarify its impact on reproductive outcomes.

Key words: ovarian stimulation, ovarian reserve, in vitro fertilization

Introduction

The primary goal of ART is to provide individualized and efficient solutions for infertile couples to achieve a live birth while minimizing adverse effects. Failures in ART contribute to treatment discontinuation due to the higher number of ovarian stimulation cycles imposing a significant financial burden and the negative impact on the couples' psychosocial well-being. Hence, ART

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aims to optimize the cumulative live birth rate per oocyte retrieval procedure. Diminished ovarian reserve (DOR) is particularly challenging as it leads to poor ovarian response (POR) during in-vitro fertilization (IVF), with a global incidence ranging from 5.6% to 35.1%.[1-2] It is more prevalent in older women, compounding age-related fertility decline and embryonic aneuploidy.

The initiation of controlled ovarian stimulation (COS) occurs in the early follicular phase, aiming for synchronized growth of early antral follicles in response to gonadotropins. Non-conventional strategies, such as DuoStim, have emerged to optimize the efficient retrieval of oocytes, particularly benefiting patients with diminished ovarian reserve (DOR) and women aiming for fertility preservation before oncologic treatment. Remarkably, late-follicular-phase stimulation yields larger cohorts of oocytes compared to early-follicular-phase stimulation, while maintaining comparable competence in blastulation and euploidy rates.[3] There are three theories regarding follicular recruitment: continuous recruitment, single recruitment episode and follicular waves.[20] The wave theory serves as the foundation for the DuoStim protocol.

Glujovsky (2020)[4] carried out a meta-analysis of non-conventional ovarian stimulation protocols and came to the conclusion that such protocols yield similar outcomes to conventional cycles, potentially with more flexibility in a shorter amount of time. Nevertheless, there is no published meta-analysis specifically focusing on double ovarian stimulation for poor ovarian responders. This study aimed to assess the effect of the double stimulation protocol (DuoStim) on poor ovarian responders in terms of cumulative live birth rates and clinical pregnancy rates, as compared to conventional stimulation protocols.

Objectives

The primary objective of the study was to determine the effect of double stimulation protocol (DuoStim) in poor responders in terms of clinical pregnancy rate and cumulative live birth rate. The secondary objective of the study was to provide a descriptive overview of the included studies and compare the effect of DuoStim versus conventional stimulation protocols in increasing cumulative live birth rates and clinical pregnancy rates of poor ovarian responders.

Methods

Systematic review and meta-analysis were performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. Inclusion criteria were limited to (1) randomized controlled trials (RCTs), cross-sectional studies, and prospective/retrospective cohort studies that (2) utilized double stimulation (DuoStim) protocol for controlled ovarian stimulation among poor ovarian responders with the (3) outcome of cumulative live birth rates and/or clinical pregnancy rates in human participants. The eligible studies (4) may or may not include other conventional ovarian stimulation protocols as comparison to the double stimulation protocol. Studies with no available full text, were written in non-English language, and those involving pediatric population (less than 19 years old) were excluded.

Search Procedure

A comprehensive search was conducted across PubMed, Cochrane, and Scopus databases, utilizing combinations of the following keywords and search terms: "double stimulation," "dual stimulation," "DuoStim," "luteal phase stimulation," "assisted reproductive technology," "ART," "poor ovarian responder," "diminished ovarian reserve," "decreased ovarian rese rve," "reduced ovarian reserve," "POSEIDON criteria," "Bologna criteria," "cumulative live birth rate," and "clinical pregnancy rate." Following predefined eligibility criteria, three reviewers screened the studies by title and abstract for initial selection. Duplicate and non-English studies were excluded. Out of the 9,954 remaining studies, eleven (11) studies fulfilled the criteria and underwent risk of bias assessment based from the Cochrane Handbook for RCT and Quality Assessment Tool for cohort and cross-sectional studies. Three of the 11 eligible studies were excluded because they lacked a conventional protocol for comparison, aiming to ensure uniformity in data analysis. Data from the 8 studies were extracted and summarized in Tables S1 and S2 (supplementary data available in digital

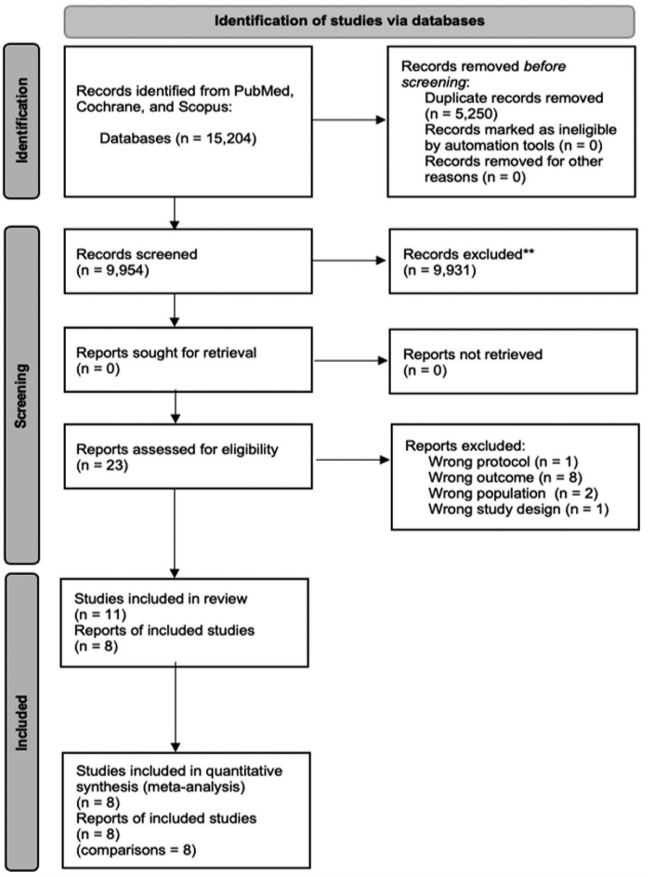

Figure 1. PRISMA flowchart for study selection

format). The study population was characterized in terms of the total number of participants, inclusion and exclusion criteria with the classification of poor ovarian response, determined either by the Bologna criteria or the POSEIDON criteria employed in the respective studies.

Data Analysis

The outcomes of interest included dichotomous variables (clinical pregnancy, cumulative live birth, and fertilization rates), for which the odds ratio (OR) and 95% confidence interval (CI) were calculated. Interstudy heterogeneity was assessed with Cochran's Q and I^2 tests. An I^2 rate exceeding 50% was an important indication of heterogeneity. When I^2 was greater than 50%, the Random effect results. If the value was less, the Fixed Effect results were considered. All of the tests were calculated on a two-tailed basis and $p<0.05$ was accepted as statistically significant. Forest plots were generated for each outcome to show variations among studies and pooled analyses. Funnel plots were generated to assess bias.

Results

Clinical Pregnancy Rate

Eight trials with 497 DuoStim participants and 1,031 conventional ovarian stimulation protocol participants reported clinical pregnancy rates in poor ovarian responders. Among the included studies, there were 5 RCTs and 3 retrospective cohort studies. Figure 2 shows that the overall estimate was 0.99 with a 95% CI of [0.75, 1.30]. The significance test of H0: $\theta = 0$ had a p-value of 0.92, which suggested that the overall effect size is not statistically significantly different from 1. Therefore, there were no significant differences in clinical pregnancy rates between poor ovarian responders who utilized DuoStim approach versus those who had conventional ovarian stimulation approach. The Q test statistic was 9.97 with a p-value of 0.19; thus, there was not enough evidence to conclude that there was significant heterogeneity between the individual studies. The I^2 indicated that about 29.8% of the variability in the effect-size estimates was due to the differences between studies.

To examine bias, a funnel plot using data from the 8 studies was done (Figure S1). The plot showed asymmetry where there was an empty space in the bottom left corner. This suggested that the smaller trials with log odds-ratio estimates close to 0 may be missing from the meta-analysis. Pilot studies, case series and case-control studies were excluded in the meta-analysis.

Data on cumulative live birth rates among poor ovarian responders using DuoStim protocol versus conventional ovarian stimulation protocol were reported in 3 studies, with 237 participants using DuoStim and 327 participants using the conventional approach. Among the included studies, there were 1 RCT and 2 retrospective cohort studies. Figure 3 shows that the overall estimate was 0.87 with a 95% CI of [0.59, 1.28]. The significance test of H0: $\theta = 0$ had a p-value of 0.47, which suggested that the overall effect size is not statistically significantly different from 1. Therefore, there were no significant differences in cumulative live birth rates between

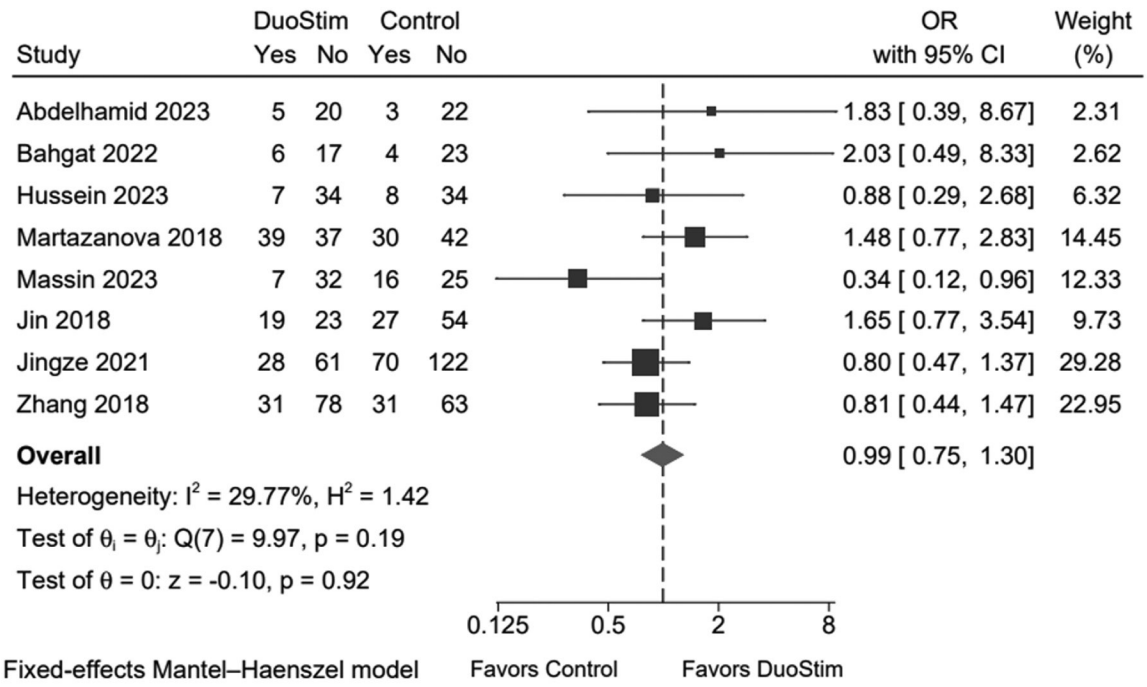

Figure 2. Forest plot of meta-analysis on clinical pregnancy rates between poor ovarian responders using double stimulation (DuoStim) and conventional ovarian stimulation.

the two groups. The Q test statistic was 2.42 with a p-value of 0.30, therefore not enough evidence to conclude that there was significant heterogeneity between the individual studies. The I^2 indicated that about 17.4% of the variability in the effect-size estimates was due to the differences between studies.

To examine bias, a funnel plot using data from the 3 studies was done and shown in supplementary data (Figure S2).

Fertilization Rate

Data regarding fertilization rates among poor ovarian responders subjected to DuoStim and conventional ovarian stimulation were documented in 5 studies, encompassing 861 cases for DuoStim and 1,146 for the conventional approach. Among these studies, there were 3 randomized controlled trials (RCTs) and 2 retrospective cohort studies. As illustrated in Figure 4, the overall estimate stands at 0.91 with a 95% confidence interval of [0.63, 1.32]. The significance test for H0: $\theta = 0$ yielded a p-value of 0.63, indicating that the overall effect size was not statistically significantly different from 1. Therefore, no significant distinctions in fertilization rates were observed between poor ovarian responders treated with DuoStim and conventional approach. The Q test statistic was 8.17 with a p-value of 0.09, indicating significant heterogeneity among the individual studies. Approximately 50.3% of the variability in effect-size estimates can be attributed to differences between studies. A subgroup analysis is recommended.

For an assessment of bias in the outcomes, a funnel plot utilizing data from 5 studies was done (Figure S3). The plot exhibited asymmetry, featuring an empty space in the lower left corner. This indication implied that larger trials with log odds-ratio estimates close to 0 might be absent from the meta-analysis.

Discussion

The Bologna criteria and the Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number (POSEIDON) classification categorized IVF cycles with poor ovarian response.[5] Studies by Hussein[6], Jin[7], Jingze[8], and Zhang[9] utilized the

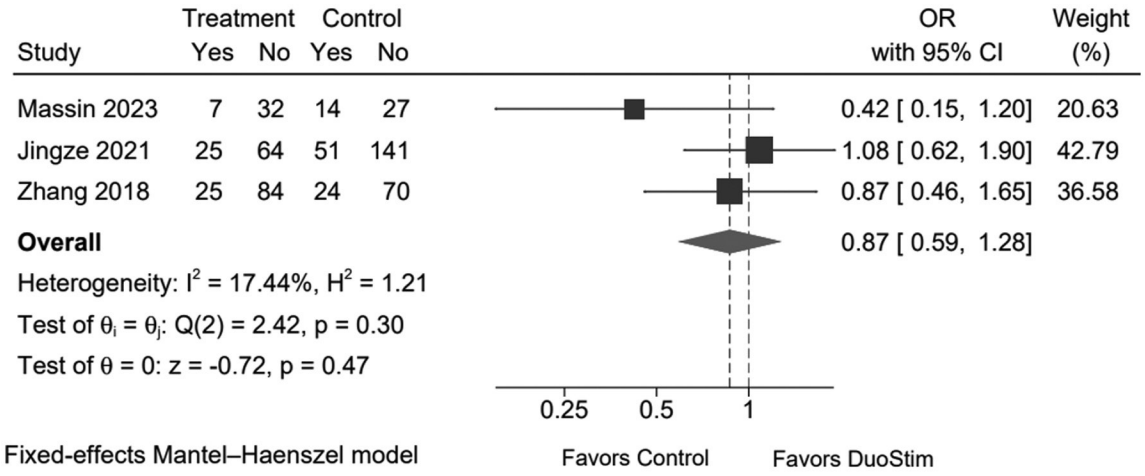

Figure 3. Forest plot of meta-analysis on cumulative live birth rates between poor ovarian responders using DuoStim and conventional ovarian stimulation.

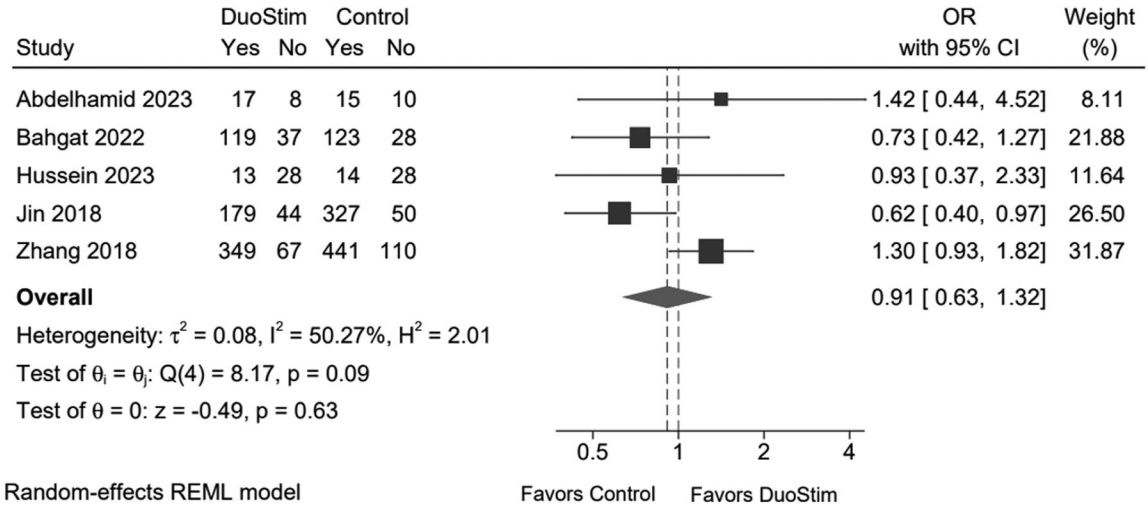

Figure 4. Forest plot of meta-analysis on fertilization rate between poor ovarian responders treated using DuoStim and conventional ovarian stimulation.

Bologna criteria as inclusion criteria. In order to satisfy the Bologna criteria for poor ovarian response (POR), a woman must demonstrate at least two of the following features: (1) advanced maternal age (≥40 years) or any other risk factor for POR; (2) a previous POR (<3 oocytes with a conventional stimulation protocol); and (3) an abnormal ovarian reserve test (AFC <5–7 follicles or AMH <0.5–1.1 ng/mL). In contrast, the POSEIDON criteria employed patient-centered methods to determine the ideal number of oocytes needed to achieve at least one euploid embryo in poor ovarian responders. It stratified the low prognosis patients in two main categories based on oocyte yield, namely, the "expected" low ovarian response (Group 3 and 4) and the "unexpected" low ovarian response (Groups 1 and 2). The four (4) groups are detailed as follows:

- Group I (younger, unexpected POR): <35 years old, AMH ≥1.2 ng/mL or AFC of ≥5, prior cycle with <10 Metaphase II retrieved
- Group II (older, unexpected POR): ≥35 years old, AMH ≥1.2 ng/mL or AFC of ≥5,

prior cycle with <10 Metaphase II retrieved
- Group III (younger, expected POR): <35 years old, AMH <1.2 ng/mL or AFC of <5
- Group IV (older, expected POR): ≥35 years old, AMH <1.2 ng/mL or AFC of <5.

Abdelhamid[10], Bahgat[11], Martazanova[12], Massin[13] employed POSEIDON criteria to include participants in their studies. The impact of ovarian reserve on euploidy rates is minimal, but it is still an important factor for predicting the availability of at least one euploid embryo for transfer. This is mainly because ovarian reserve affects the number of oocytes obtained.

The cumulative live birth rate (CLBR) per cycle is regarded as a crucial indicator of success in IVF.[14] The number of oocytes obtained after controlled ovarian stimulation (COS) has significant impact in the clinical outcome.[15-17] Hence, it is crucial to optimize the amount of oocytes based on the ovarian reserve of each patient. The outcome for individuals with poor ovarian response can vary greatly depending on factors such as age and the number of oocytes extracted.

An optimal ovarian stimulation protocol for in-vitro fertilization (IVF) should (1) demonstrate low cancellation rate, (2) minimize drug costs, risks, and side effects, (3) require limited monitoring for practical convenience, and (4) maximize the cumulative live birth rate per oocyte retrieval procedure, which refers to the overall probability of achieving one or more live births after utilizing all fresh and frozen embryos generated from a single oocyte retrieval. Vaiarelli[18] suggested that ideal number of retrieved oocytes after controlled ovarian stimulation is between 10 and 15 to increase the likelihood of a live birth rate in fresh embryo transfer cycles. The ultimate goal of ART is the successful delivery of a single pregnancy at term.

Conventional Stimulation Protocols

The European Society of Human Reproduction and Embryology (ESHRE) of 2019 reported that GnRH agonists and antagonists treat poor ovarian response similarly in safety and efficacy.[19] Five of the eight trials employed GnRH antagonists during the follicular phase as controls. The DuoStim method demonstrated a higher efficacy in oocyte retrieval compared to the GnRH antagonist protocol. However, the study conducted by Massin (2023) showed that the Duostim group had a noticeably reduced clinical pregnancy rate compared to the people who had 2 consecutive cycles of the GnRH antagonist protocol.[13]

Jalamudin (2019)[20] suggested mild stimulation protocol for managing POR, citing an increased live birth rate despite a low oocyte yield. The Practice Committee of the American Society of Reproductive Medicine (ASRM) endorsed minimal ovarian stimulation as an option for treating patients with poor ovarian response (POR) due to its equivalent success rates with lower dosages and costs. Recent studies by Zhang (2018)[9] and Jingze (2021)[8] employed mild stimulation protocols in their control groups. The results demonstrated similar outcomes with DuoStim in regards to the number of oocytes retrieved, clinical pregnancy rate, and live birth rate.

Lensen et al.[21] conducted a comprehensive Cochrane meta-analysis of gonadotropin doses for poor ovarian response (POR) in 2017. Gonadotropins above 150 IU retrieved more oocytes in poor ovarian responders with no increase in live births and ongoing pregnancies. Cumulative increase of gonadotropin doses were documented in DuoStim protocols due the frequency of stimulations within the cycle. Hussein and Jingze found that the DouStim group had significantly higher gonadotropin duration, dosage, > 14 mm sized follicle count, and serum levels of luteinizing hormone, estradiol, and progesterone on the trigger day compared to the two consecutive mild stimulations group. Nevertheless, there was no substantial disparity in the quantity of oocytes obtained between the two groups ($p > 0.05$). A retrospective study by Luo, et al.[22] compared the effects of trigger drugs (urine human chorionic gonadotropin or uhCG, recombinant hCG, and GnRH agonist) at the follicular phase and luteal phase of DuoStim protocol among poor ovarian responders (POR). There was a larger number of retrieved oocytes and good-quality embryos at the luteal phase stimulation than at the follicular phase. Recombinant hCG and GnRH agonist produced more cryopreserved, high-quality embryos than urinary HCG regardless of phase.

Double or Dual Stimulation Protocol (DuoStim)

The DuoStim method can increase the number of recovered oocytes and blastocysts of poor ovarian responders in one cycle.[23] In both FPS and LPS, the patients are given the maximum dose of recombinant FSH (300 IU/day) plus recombinant LH (150 IU/day) using the GnRH antagonist protocol. The second stimulation commenced five days subsequent to the first retrieval. Further studies suggest that a greater number of Metaphase II (MII) oocytes can be retrieved at LPS than FPS.[24] Therefore, maximizing the number of oocytes in these patients could significantly increase the chances of obtaining a competent embryo per menstrual cycle compared to conventional stimulation. All but one of the included studies showed significant increase in the number of MII oocytes in the DuoStim group.

During the luteal phase stimulation of DuoStim approach, the quantity of oocytes obtained is either equivalent to or higher than that observed with follicular-phase stimulation alone.[25] This was evident in the studies of Hussein[6], Jin[7], Zhang[9], and Luo[22]. Enhanced estrogen and progesterone levels during LPS may contribute to a greater degree of synchronization in follicular development. An alternative hypothesis posits that the in vivo environment during the LPS stage could potentially augment angiogenic factors, consequently increasing the granulocytes' responsiveness to follicle-stimulating hormone (FSH).[26] Furthermore, a potential flare-up effect could arise from the stimulation of the follicular phase with a gonadotropin-releasing hormone (GnRH) agonist trigger. This could lead to a reduction in the expression of anti-Müllerian hormone (AMH) in the follicles, beginning with the anovulatory wave. As a consequence, the quantity of follicles measuring 3–4 mm in diameter that are recruited during LPS may increase.[22]

Current DELPHI consensus[30] recommended utilizing DuoStim only in patients requiring immediate oocyte retrieval, such as those undergoing oocyte cryopreservation, of advanced maternal age or with reduced ovarian reserve. Recognizing that the number of retrieved oocytes per ovarian stimulation cycle significantly impacts cumulative live birth rates, DuoStim proves to be an effective method for optimizing outcomes in poor ovarian responders.

Conclusion

Current evidence does not demonstrate significant superiority of DuoStim over conventional ovarian stimulation protocols in terms of clinical pregnancy rates, cumulative live birth rates, or fertilization rates among poor ovarian responders. However, DuoStim appears to be an effective strategy for increasing oocyte yield within a shorter treatment timeframe. Its use may be particularly relevant in selected patients with diminished ovarian reserve, advanced maternal age, or urgent fertility preservation needs. Further high-quality prospective trials are warranted to clarify its impact on reproductive outcomes.

Despite the paucity of statistically significant data supporting the effect of DuoStim in the clinical pregnancy rates and cumulative live birth rates of poor ovarian responders, it remains to be a promising alternative approach to augment the number of oocytes that are available for fertilization. It addresses the challenge of decreased ovarian reserve and has the potential to increase the number of pregnancies and live births. DuoStim has limitations, including mandatory freeze-all approach and lack of cost-effectiveness data. Further randomized controlled trials or prospective cohorts are required to fully understand the role of DuoStim in poor ovarian responders (PORs).

Limitations of the Study

The meta-analysis excluded case series, case-control studies, and pilot studies. Recommendations include (1) implementing a multicenter study to encompass a broader population, and (2) including all study designs pertinent to the aims of the investigation.

Conflict of Interest

The financial requirements of the study was shouldered by the principal investigator. The authors' opinions do not necessarily reflect that of the authors' institutions. The investigators have no conflict of interest to declare.

Ethics Approval

The study was exempted from ethics approval by University of the Philippines Manila Research Ethics Board (UPMREB) Review Panel 3 last January 4, 2024 with reference number 2023-0831-EX.

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