Systematic Review

Comparing Clinical Outcomes Between Flexible and Fixed Progestin-Primed Ovarian Stimulation

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Abstract

Controlled ovarian stimulation (COS) is essential in assisted reproductive technology (ART) to obtain multiple oocytes. Gonadotropin-releasing hormone (GnRH) analogues have been used to prevent the premature luteinizing hormone (LH) surges. However, daily injections and high cost cause inconvenience and limit patients' adherence. Recently, progestin-primed ovarian stimulation (PPOS) has emerged as an alternative. However, the optimal timing of progesterone administration remains unclear. This systematic review aimed to compare clinical outcomes between a fixed regimen that initiates progestin at the beginning of the cycle and a flexible regimen that initiates progestin later in the cycle. A comprehensive literature search was conducted in PubMed, Cochrane, Medline, and Embase Library to identify relevant studies published between January 2018 and April 2024. It was supplemented by manual searches, which identified 3 eligible retrospective cohort studies directly comparing fixed and flexible PPOS protocols. Selected studies were systematically appraised. Two studies in women with diminished ovarian reserve (DOR) found no significant differences between the two regimens, whereas one study in poor ovarian responders (POR) found a higher cumulative live birth rate (CLBR) and lower progesterone use in the flexible group, especially in older, low-prognosis women. Flexible and fixed PPOS regimens show comparable outcomes in DOR patients. Still, preliminary evidence shows potential advantages of the flexible timing in women with advanced age or POR. Therefore, future large-scale prospective studies are needed to validate these findings.
Keywords: *progestin-primed ovarian stimulation, flexible PPOS, fixed PPOS, in vitro fertilization, poor ovarian response.*

Perbandingan Luaran Klinis antara Stimulasi Ovarium Berbasis Progestin Fleksibel dan Tetap

Abstrak

Stimulasi ovarium terkontrol (SOT) merupakan komponen penting dalam teknologi reproduksi berbantu (TRB) untuk memperoleh beberapa oosit. Analog gonadotropin-releasing hormone (GnRH) digunakan untuk mencegah lonjakan luteinizing hormone (LH) prematur, namun memerlukan injeksi harian dan biaya tinggi sehingga menurunkan kepatuhan pasien. Protokol stimulasi ovarium berbasis progestin (progestin-primed ovarian stimulation/PPOS) kini menjadi alternatif, tetapi waktu pemberian progesteron yang optimal masih belum jelas. Tinjauan sistematis ini bertujuan membandingkan luaran klinis antara regimen tetap yang memulai progestin sejak awal siklus dengan regimen fleksibel yang memberikan progestin di tengah siklus. Pencarian pada empat basis data utama (PubMed, Cochrane, Medline, Embase) serta penelusuran manual mengidentifikasi tiga studi kohort retrospektif yang membandingkan PPOS tetap dan fleksibel. Studi terpilih dievaluasi secara sistematis. Dua studi pada wanita dengan cadangan ovarium menurun (diminished ovarian reserve/DOR) menunjukkan tidak ada perbedaan bermakna. Satu studi pada pasien dengan respons ovarium buruk (poor ovarian responders/POR) melaporkan angka kelahiran hidup kumulatif (cumulative live birth rate/CLBR) yang lebih tinggi dan dosis progesteron lebih rendah pada kelompok fleksibel, terutama pada wanita usia lanjut dengan prognosis rendah. PPOS tetap dan fleksibel memberikan luaran serupa pada pasien DOR. Namun, temuan awal menunjukkan potensi keunggulan protokol fleksibel pada wanita usia lanjut atau dengan POR, sehingga diperlukan studi prospektif berskala besar untuk mengonfirmasi.
Kata kunci: *stimulasi ovarium yang diinisiasi progestin, SPO fleksibel, SPO tetap, fertilisasi in vitro, respons ovarium yang buruk.*

Introduction

Controlled ovarian stimulation (COS) is an important part of assisted reproductive technology (ART). Its goal is to produce several oocytes to improve embryo yield and the chances of pregnancy.[1] In the past, doctors have used gonadotropin-releasing hormone (GnRH) analogues, such as GnRH agonists or antagonists, during COS to prevent early luteinizing hormone (LH) surges. These surges can cause early ovulation and lower the success of ART. However, daily injections and high costs can make treatment uncomfortable and reduce how well patients stick to it.[1,2]

Recently, progestin-primed ovarian stimulation (PPOS) has become a promising and more convenient alternative to GnRH analogues.[3,4] PPOS uses oral progestin to prevent early LH surges during ovarian stimulation and achieves similar results in oocyte retrieval, embryo quality, and pregnancy rates.[5] It works well for women with different levels of ovarian reserve, from diminished (DOR) to normal (NOR), is more cost-effective, and is especially useful when planning freeze-all embryo transfer strategies.[2,6]

There are still key questions about when to give progesterone in PPOS protocols. Researchers have mainly studied two types: fixed and flexible.[1,7] In fixed PPOS, progestin starts at the beginning of ovarian stimulation. Meanwhile, in flexible PPOS, progestin is given later, once certain criteria such as follicle size or estradiol levels are reached.[6] Recent studies have compared these two methods, especially in patients with poor ovarian response (POR) or diminished ovarian reserve (DOR), where finding the best treatment is important because success rates are usually lower in these groups.[1,8,9]

Recent studies also show that both fixed and flexible PPOS protocols give similar results for women with diminished ovarian reserve (DOR), such as the number of eggs collected and the rate of premature LH surge.[8] However, some studies suggest that the flexible protocol may be better for women with poor ovarian response (POR) or older age, as it can lead to higher overall live birth rates, less exposure to progestin, improve treatment, and become a more comfortable choice for these groups.[9]

Given the advantages and increasing use of PPOS in ART over traditional GnRH analogues protocols. It is essential to systematically evaluate the comparative effectiveness of fixed versus flexible PPOS regimens. This review aims to synthesize clinical evidence from the last five years to clarify the optimal PPOS strategy for various patient groups. The results of this review will guide clinicians in tailoring PPOS protocols in the future to increase ART success rates, improve patient comfort, and reduce costs.

Methods

Study Design and Population

This study was conducted as a systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10] The review aimed to compare the clinical outcomes between flexible and fixed PPOS among women undergoing ART cycles.

PICO Framework

To guide the review, the following PICO components were defined:[11] Population (P): Patients with either POR or DOR undergoing IVF/ICSI, assisted reproductive technology; Intervention (I): Flexible regimen of PPOS (started later in the cycle depending on follicular growth); Comparison (C): Fixed regimen of PPOS (started from early along the gonadotropins; Outcomes (O): Primary: total oocyte yield, number of metaphase II (MII) oocytes; Secondary: cumulative live birth rate (CLBR), number of two pronuclei (2PN) embryos, number of viable embryos per cycle, incidence of premature LH surge, length of stimulation, and dose of gonadotropin.

Search Strategy

A comprehensive literature search was conducted in PubMed, Cochrane, Medline, and Embase Library to identify relevant studies published between January 2018 and April 2024. The search strategy combined Medical Subject Headings (MeSH) and free text keywords related

to ART and PPOS, including terms such as “in vitro fertilization”, “IVF”, “intracytoplasmic sperm injection”, “ICSI”, “assisted reproduction”, “ART”, “ovulation induction”, “ovarian stimulation”, “flexible progestin primed ovarian stimulation”, “flexible PPOS”, “fixed progestin primed ovarian stimulation,” “fixed PPOS”, “conventional”, “regular”, “efficacy”, “oocyte”, “embryo”, “ovarian hyperstimulation syndrome”, “OHSS”, “premature luteinization”, and “premature LH surge”. Boolean operators (AND/OR) were used to combine search terms appropriately, and reference lists of included studies were manually screened to identify additional eligible articles.

Inclusion and Exclusion Criteria

Inclusion criteria included original studies published in English that involved human participants undergoing IVF/ICSI treatment and that provided a direct comparison between flexible and fixed PPOS protocols. Excluded studies included case reports, editorials, or narrative reviews that lacked a direct comparison between flexible and fixed PPOS protocols or focused on non-PPOS stimulation protocols.

Study Selection and Variability

A comprehensive search of 4 databases (PubMed, Cochrane, Medline, and Embase) and manual hand-searching resulted in nine records. No duplicate records were found. Following title and abstract screening, four studies were excluded due to unsuitable study designs. The remaining five studies underwent full-text evaluation; two were excluded because one used the wrong comparison and another was a preliminary abstract. Therefore, three retrospective cohort studies met the inclusion criteria and were included in the final review. As all included studies were retrospective cohort studies, methodological variability was limited. Sensitivity analyses were performed when necessary to address potential bias arising from differences in study design.

Outcome Measures and Definitions

The primary outcomes of this systematic review were the number of oocytes retrieved and the number of metaphase II (MII) oocytes retrieved. These outcomes reflect the ovarian response to stimulation and the proportion of oocytes that have reached full maturation, both of which are key indicators of the effectiveness of the stimulation protocol.

The secondary outcomes included the CLBR, the number of 2PN embryos, the number of viable embryos per cycle, the incidence of premature LH surge, the length of stimulation, and the gonadotropin dose. These outcomes assess the overall clinical effectiveness and reproductive potential of each protocol, comprising both embryology and endocrine parameters. The incidence of premature LH surge refers to an early increase in serum LH levels during COS, which was evaluated to determine endocrine stability and the degree of pituitary suppression achieved by each protocol.

Additional outcomes reported in individual studies that were not consistently available across all included studies were also extracted and narratively summarized when relevant. All outcome measures were defined and interpreted according to standard clinical practice and as reported within the methodologies of the respective studies.

Risk of Bias Assessments

Each included study was independently evaluated using the Cochrane Risk of Bias Assessment Tool.[12] This tool covers seven key domains: (1) Bias due to confounding; (2) Bias due to selection of participants; (3) Bias in classification of interventions; (4) Bias due to deviations from intended interventions; (5) Bias due to missing data; (6) Bias in measurement of outcomes; and (7) Bias in selection of the reported result. Each domain is categorized as low risk, moderate risk, serious risk, critical risk, or no information, depending on the quality of the reporting and methodological rigor.

Statistical Analysis

Due to the heterogeneity of each included study and variations in outcome reporting, data were synthesized qualitatively. Data extracted from the full text, tables, graphs, and references

were compiled to enable comparative analysis between fixed and flexible protocols. A meta-analysis was not performed due to the limited availability of comparable datasets across studies.

Results

Nine records were initially retrieved from a comprehensive search of PubMed, Cochrane, Medline, and Embase databases. After initial screening, four studies were excluded due to unsuitable study designs. The remaining articles underwent full-text review, yielding three retrospective cohort studies that met the inclusion criteria. The study selection flow chart is summarized in the PRISMA figure below (Figure 1).

A total of three retrospective cohort studies, comprising 640 women with either diminished ovarian reserve or poor ovarian response, compared the effectiveness of fixed- and flexible-PPOS regimens. The progestins used in these studies were either medroxyprogesterone acetate (MPA) or dydrogesterone (DYG). Dosing of progestin, as well as the cut-off for progesterone initiation in flexible PPOS, including follicle size and estradiol levels, varied slightly across studies. A summary of the characteristics of the included studies is presented in Table 1.

Both studies by Kalafat et al[7] and Doğan Durdağ et al[8] showed no significant differences between fixed and flexible PPOS regimens in the total number of oocytes and the number of mature (MII) oocytes retrieved. They suggested that the timing of progesterone initiation did not significantly affect oocyte yield. On the other hand, Chen et al[9] found that the flexible regimen

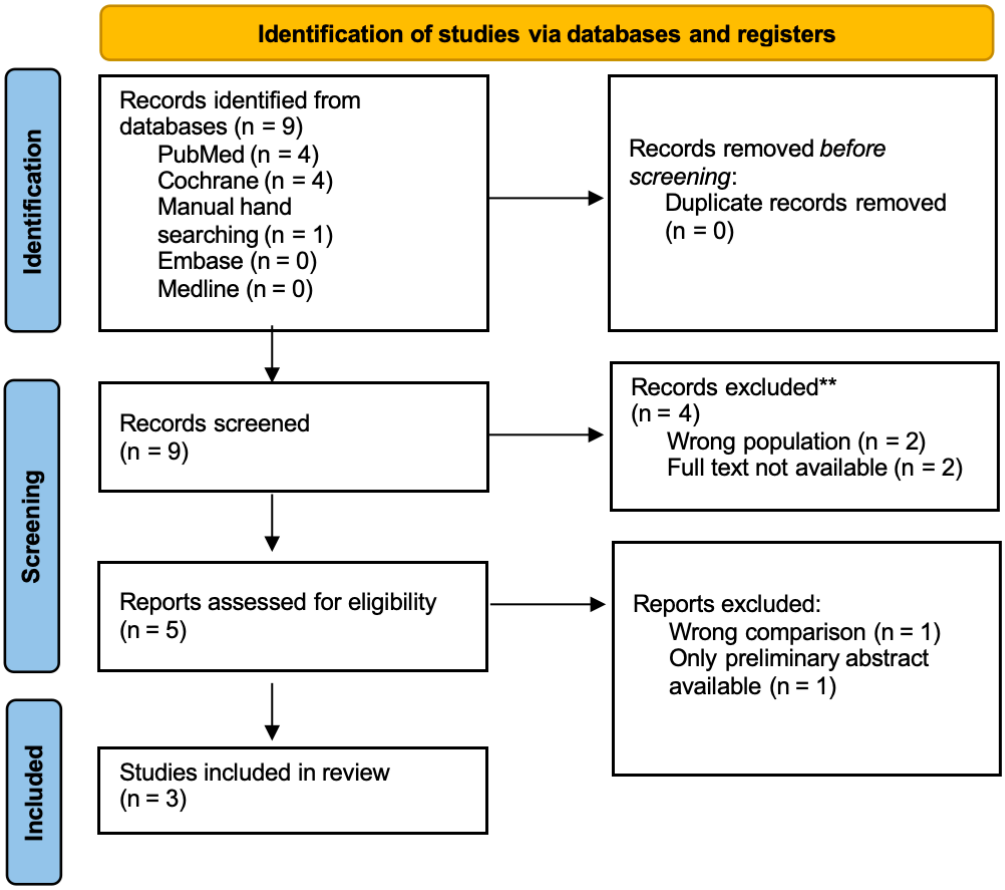

Figure 1. PRISMA Flowchart for Study Screening and Selection

resulted in significantly higher MII oocyte rate (89.8% vs. 84.7%, p = 0.016) but fewer total oocytes (3.20 ± 2.14 vs. 4.45 ± 2.75, p <0.001), MII oocytes (2.87 ± 2.03 vs. 3.76 ± 2.32, p <0.001), and number of 2PN embryos.[9] These, however, did not translate to significant differences in clinical outcomes except in Group 4 (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) Poseidon criteria. In women aged ≥35 years with poor ovarian reserve, Chen et al[9] found that the CLBR was significantly higher in the flexible regimen group than in the fixed regimen group (34.6% vs. 14.8%, p = 0.024).[7-9]

All studies consistently demonstrated that both PPOS regimens effectively suppressed premature LH surge. The incidence of premature LH surge or luteinization was low and did not differ significantly between fixed and flexible groups, confirming adequate pituitary suppression with either protocol. Moreover, across all studies, there was no significant difference in the duration of stimulation or the gonadotropin dose administered.[7-9] Regarding total dosage of progestin given, Chen et al[9] reported that the total MPA consumption in the flexible regimen was significantly lower compared to that of the fixed regimen (75.61 ± 29.34 vs. 120.20 ± 23.54, p <0.001).[9]

All three included retrospective cohort studies demonstrated low to moderate risk of bias across assessed domains (Figure 2). Confounding bias varied: moderate in Kalafat et al[7] and Durdag et al[8], and low in Chen et al.[9] due to propensity score matching (age, BMI, AFC, AMH, infertility type). Selection bias varied by sample-size balance, with moderate risk in Kalafat et al[7] and Durdag et al[8], and serious risk in Chen et al[9] due to unequal group sizes. Biases related to intervention classification and deviations from intended interventions were consistently low, and missing-data bias was generally low across studies, with transparent reporting of exclusions in Kalafat et al.[9] Overall, interventions, outcome measurement, and reporting bias were low due to standardized and comprehensively reported outcomes.

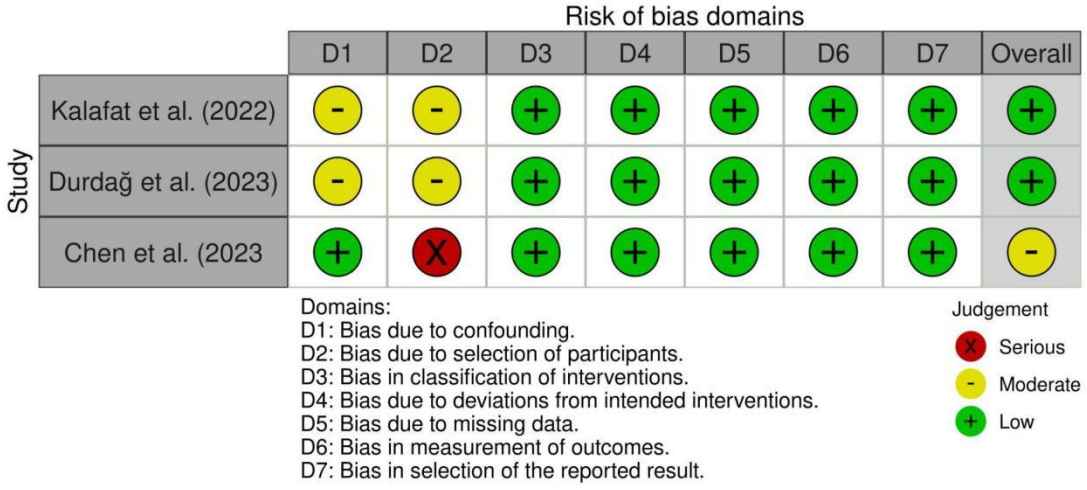

Figure 2. Risk of Bias Summary

Table 1. Main Study Characteristics of Included Studies

Studies	Study Design	Study's Setting	Sample Size (n)	Interventions	Measured Endpoints	Results	Conclusion
Kalafat et al[7]	Retrospective cohort	Nulligravid women with DOR undergoing elective oocyte cryopreservation in ART at Koc University Hospital (Turkey) between July 2018 and August 2021	90	**Fixed PPOS regimen (n = 30)** Medroxyprogesterone acetate (MPA) 10 mg/day p.o. given simultaneously with 300 IU/day recombinant follicle-stimulating hormone (rFSH) from the early stage of the cycle **Flexible PPOS regimen (n = 60)** MPA 10 mg/day p.o. started later in the cycle (i.e., when leading follicle ≥ 14 mm OR serum estradiol (E2) >200 ng/mL)	**Primary:** N of oocytes and MII oocytes retrieved per cycle **Secondary:** Premature LH surge (>10 ng/mL), N of follicles >14 mm on the day of maturation trigger	No significant differences were found between the two cohorts regarding the number of MII oocytes retrieved, the incidence of premature LH surge, and the number of follicles larger than 14 mm on the day of maturation trigger.	Fixed and flexible PPOS regimens yielded similar oocyte yields and a low rate of premature ovulation, suggesting that both regimens can be effectively used in patients with DOR.
Durdag et al[8]	Retrospective cohort	Women with DOR in a tertiary center in Turkey between January 2019 and June 2022	125	**Fixed PPOS regimen (n = 83)** Dydrogesterone (DYG) 20 mg/day p.o. given simultaneously with 150-300 IU/day gonadotropin (human menopausal gonadotropin (HMG) and/or rFSH from the early stage of the cycle **Flexible PPOS regimen (n = 42)** DYG 20 mg/day p.o. started later in the cycle (i.e., when leading follicle ≥ 12 mm OR serum estradiol (E2) >200 pg/mL)	**Primary:** Premature luteinization rate **Secondary:** Length of stimulation, gonadotropin dose administered, N of oocytes and MII oocytes, fertilization rate, clinical pregnancy rate	There were no significant differences found between fixed and flexible PPOS cycles regarding the rate of premature luteinization, length of stimulation, total gonadotropin dose administered, total number of oocytes, number of MII oocytes retrieved, rate of fertilization, and rate of clinical pregnancy	Both fixed and flexible PPOS regimens were similarly effective in preventing premature luteinization and improving other ovarian stimulation parameters.

Table 1. Main Study Characteristics of Included Studies (Continue)

Studies	Study Design	Study's Setting	Sample Size (n)	Interventions	Measured Endpoints	Results	Conclusion
Chen et al[9]	Retrospective cohort	Women with POR undergoing IVF/ICSI in the reproductive center of Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China, between January 2018 and December 2020	425	**Conventional/fixed PPOS regimen (n = 318)** MPA 10 mg/day p.o. given simultaneously with 150-300 IU/day gonadotropin from the early stage of the cycle **Flexible PPOS regimen (n = 107)** MPA 10 mg/day p.o. started later in the cycle (i.e., when leading follicle ≥ 12 mm OR serum estradiol (E2) >200 pg/mL)	**Primary:** Cumulative live birth rate (CLBR) **Secondary:** Cumulative pregnancy rate (CPR), N of oocytes retrieved, N of MII oocytes, available embryos, MII oocytes rate, two pronuclei (2PN) embryos rate, length of stimulation, gonadotropin dose administered, premature LH surge, cancellation rate, follicular output rate (FORT), follicle-to-oocyte (FOI), blastocyst rate	The flexible PPOS cohort had a significantly higher MII oocyte rate but fewer retrieved oocytes, MII oocytes, and 2PN embryos than the fixed PPOS cohort. Women aged ≥35 years with POR (low-prognosis patients) who underwent the flexible regimen achieved significantly higher CLBR than their counterparts who got the fixed regimen (34.6% vs 14.8%, p = 0.024) The total dose of MPA was significantly lower in the flexible PPOS cohort compared to the fixed PPOS cohort (75.61 IU vs 120.20 IU) Other outcomes were comparable between the two cohorts.	Flexible PPOS regimen appeared to be more favorable than the fixed PPOS regimen in achieving pregnancy whilst requiring less MPA consumption for low-prognosis women undergoing ovarian stimulation.

Discussion

This systematic review highlights the comparable efficacy of fixed and flexible PPOS regimens in women with impaired ovarian function undergoing assisted reproductive treatment. Across the included studies, both approaches yielded similar numbers of total and MII oocytes and effectively prevented premature LH surges.

A previous study by Lin et al,[13] suggested that the PPOS protocol can improve ART outcomes in women with DOR. However, the comparative effect between flexible and fixed PPOS regimens within this population remains poorly established.[13] Among the included studies, flexible and fixed PPOS regimens showed comparable outcomes in DOR patients for oocyte yield, oocyte maturity, and effectiveness in preventing premature LH surge. Notably, Chen et al[9] identified a potential subgroup benefit associated with flexible PPOS protocols. Women in the POSEIDON group 4 achieved significantly higher CLBR with the flexible regimen than with the fixed regimen (34.6% vs. 14.8%, p = 0.024), despite receiving a significantly lower total MPA dose (75.61 ± 29.34 vs. 120.20 ± 23.54, p <0.001).[9] Matsuda et al.[14] reported similar trends among poor ovarian responders, in which the flexible PPOS protocol yielded more oocytes than the fixed PPOS protocol. This may be due to the lower total progestin dose and the delayed initiation of progestins, which may optimize follicular development and improve outcomes.[14] These findings are particularly relevant to POSEIDON Groups 3 and 4, which are the poor-prognosis subgroup. They have a significantly reduced ovarian reserve, a limited number of recruitable follicles, and an age-related decline in oocyte quality. These biological issues lower the chances of producing chromosomally normal embryos and achieving live birth.[15,16] Therefore, the findings from Chen et al[9] and Matsuda et al[14] show the promise of novel, more effective, and personalized treatment strategies to improve outcomes in this high-risk group.[9,14]

The flexible PPOS regimen may be preferable to a fixed regimen for safety and adverse outcomes, as it allows a lower total progestin dose and a shorter duration of progesterone exposure. Unlike the fixed PPOS protocol, the flexible PPOS protocol allows progestins such as MPA or DYG to be administered only after the leading follicle reaches a certain size or when serum estradiol reaches a specific cut-off level. Findings from Chen et al.[9] suggested that a flexible regimen could result in a shorter duration of progestin exposure and, consequently, lower progesterone levels during the follicular phase. Past evidence had associated high progesterone levels with impaired oocyte quality, implantation rate, and CLBR, particularly when the concentration exceeds 1 ng/mL.[17,18] The biological mechanisms behind how high progesterone levels lead to poor oocyte quality remain poorly understood, with several theories pointing towards effects on oocyte maturation, fertilization, and embryonic developmental milestones.[19,20] Currently, there is no clear consensus on the cut-off level for progesterone considered too high. A value of 1.5 ng/mL prior to hCG trigger administration is often adopted as a general estimate to predict pregnancy outcomes.[21] However, it also depends on each patient's condition and ovarian response, such as whether they are poor, normal, or high responders.[20]

While Pitner et al[22] also proposed that a longer duration of elevated progesterone exposure could be detrimental to IVF cycles, other studies produced mixed results.[22] Data from Zhang et al[23] showed that longer exposure to elevated progesterone levels (i.e., 1 day versus ≥ 2 days) did not significantly affect clinical pregnancy rate. It was hypothesized that prolonged exposure might alter the implantation window, leading to asynchrony between the embryo transfer and the endometrium.[23] More research is needed to clarify this conflicting evidence. In the PPOS regimen, however, the mandatory use of a freeze-all strategy cancels the adverse effect of prolonged elevated progesterone levels, which would otherwise compromise endometrial receptivity in a fresh transfer cycle.[3]

Previous studies have consistently demonstrated that the PPOS protocol is more cost-effective than the conventional GnRH antagonist protocols. This is primarily due to the use of oral progestins, which significantly reduce medication costs compared to the expensive daily injection by lowering the overall cost per cycle and per mature oocyte. In addition, oral administration also enhances patient comfort and compliance by eliminating the need for daily injections, while maintaining comparable safety and efficacy outcomes, especially in freeze-all cycles.[24,25] Furthermore, the flexible PPOS regimen offers even greater cost savings and tolerability by initiating progestin based on specific follicular growth and estradiol levels. This approach reduces total drug exposure without affecting cycle outcomes.[7] Among the included studies, Chen et al[9] highlighted this potential benefit, suggesting a personalized and physiology-based ART strategy could improve pregnancy outcomes in a more cost-effective and patient-friendly way, using a lower total progestin dose.[9]

Future studies should focus on validating this review's findings on a large scale, with subgroup analyses based on ovarian reserve and POSEIDON classification to determine the optimal timing of progestin initiation.

Conclusion

Taken together, our systematic review summarizes the latest evidence indicating that both fixed and flexible PPOS regimens provide equivalent outcomes in terms of oocyte yield, maturity, and effectiveness in preventing premature LH surges. However, among low-prognosis women, the flexible regimen may offer an advantage in improving cumulative live birth outcomes while requiring lower total progestin consumption.

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Authors' Contributions

The contributions of each author are as follows. Concept and design by R Muharam, Edward Christopher Yo, Alisha Nurdya Irzanti. Acquisition of data or sampling by R Muharam, Edward Christopher Yo, Tasya Kartika, Alisha Nurdya Irzanti. Analysis and data interpretation by R Muharam, Edward Christopher Yo, Tasya Kartika, Alisha Nurdya Irzanti, Achmad Kemal Harzif, Mila Maidarti, Gita Pratama, Kanadi Sumapraja, Andon Hestiantoro, Budi Wiweko. Drafting the article by R Muharam, Edward Christopher Yo, Tasya Kartika. Critically revising and approving the final version to be published by R Muharam, Edward Christopher Yo, Tasya Kartika, Alisha Nurdya Irzanti, Achmad Kemal Harzif, Mila Maidarti, Gita Pratama, Kanadi Sumapraja, Andon Hestiantoro, and Budi Wiweko.

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Competing Interests

The authors have no conflict of interest related to this publication.

AI Usage Declaration

No artificial intelligence tools were used during the research or manuscript preparation in this publication. All content has been reviewed, verified, and approved by authors, and full responsibility for the manuscript remains with the authors.

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