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Review

A Narrative Review of Progestin-Primed Ovarian Stimulation Protocols in Ovaries: Current Trends and Perspectives

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Abstract

Objective: This review aimed to provide an updated overview of progestin-primed ovarian stimulation (PPOS) outcomes across different patient groups, particularly in egg donation, fertility preservation, preimplantation genetic testing (PGT), and endometriosis. **Mechanism**: We performed a focused narrative review of the literature in the PubMed/MEDLINE databases, identifying randomized trials, cohort studies, systematic reviews, and meta-analyses comparing PPOS to gonadotropin-releasing hormone (GnRH) agonist and GnRH-antagonist protocols (search completed to April 2025). Selection emphasized high-quality evidence and recent comprehensive reviews across different patient groups. **Findings in Brief**: PPOS demonstrated efficacy across various clinical scenarios, including oocyte donation, fertility preservation, PGT, polycystic ovary syndrome (PCOS), low and high ovarian responses, and endometriosis. While overall neonatal safety is acceptable, some concerns persist regarding specific progestins, such as dydrogesterone. **Conclusions**: PPOS protocols represent valid, non-inferior alternatives to GnRH antagonists in various clinical populations when an oocyte- or embryo-freezing strategy is employed.

Keywords: PPOS; progestins; LH; ovarian stimulation protocols; GnRH antagonists; fertility preservation; preimplantation genetic testing

1. Introduction

Ovarian stimulation (OS) is a fundamental component of assisted reproductive technology (ART) treatments, aiming to obtain an optimal number of mature oocytes to maximize the generation of viable embryos. A crucial challenge in this process is to prevent premature ovulation triggered by a premature luteinizing hormone (LH) peak in response to an estradiol surge during multi-follicular development [1]. In the absence of pituitary suppression, this phenomenon occurs in approximately 20% of ovarian stimulation cycles, compromising the retrieval of metaphase II (MII) oocytes and decreasing treatment success rates [2].

Over time, various strategies have been developed to optimize OS outcomes, improving the safety and efficacy of treatments. Initially, the long gonadotropin-releasing hormone (GnRH) agonist protocol became the standard, enabling effective control of the LH surge by profoundly suppressing the hypothalamic-pituitary-gonadal axis [3]. However, this protocol contains disadvantages, such as a longer duration of treatment and increased risk of ovarian hyperstimulation syndrome (OHSS), as an agonist trigger cannot be used [3]. Subsequently, the introduction of GnRH antagonists significantly reduced protocol duration, costs, and the need for daily injections, thereby improving treatment adherence [3].

More recently, a new strategy using progestins to inhibit the LH peak has emerged, leading to the progestin-primed ovarian stimulation (PPOS) protocol [4]. This approach, initially described by Kuang *et al*. [4], is based on the ability of progesterone to suppress LH release by inhibiting estradiol-sensitive cells in the hypothalamus [5], inspired by the gonadotropin suppression observed during the luteal phase [5]. Kuang *et al*. [4] effectively prevented the premature LH surge and early ovulation by administering 10 mg/day of medroxyprogesterone acetate (MPA) in combination with gonadotropins [4]. Subsequently, various progestins and micronized progesterone have been evaluated in PPOS cycles, consolidating this approach as a valid alternative to traditional protocols using GnRH analogs [1,6].

The exact mechanism by which progesterone suppresses gonadotropin secretion has not yet been fully elucidated [7]. However, evidence suggests that this effect is mainly due to hypothalamic action that interferes with the typical estradiol-mediated response [7].

PPOS protocols are beneficial in scenarios where a receptive endometrium is unnecessary, such as in fertility preservation, oocyte donation, delayed embryo transfer, and preimplantation genetic screening [8,9]. In addition, multiple studies have reported that PPOS yields a comparable number of oocytes with reproductive potential similar to that of GnRH analog protocols, with no significant differences in fertilization rates, blastocyst development, or euploidy [1,6].

However, despite the advantages of PPOS, this technique might not be suitable for all patients. In particular,

the use of progestins may pose an additional risk in women with progesterone receptor-positive breast cancer [10,11].

Thus, this narrative review provides an overview of PPOS protocols, covering their mechanism of action, types, advantages and limitations, clinical applications in various patient populations, and evidence on neonatal safety, while highlighting recent findings and future research directions

2. Literature Review

A literature search was conducted through April 2025 to identify studies evaluating PPOS protocol outcomes in *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI) across different patient populations. Keywords used included "PPOS", "progestin-primed ovarian stimulation", "IVF outcomes", "poor ovarian responders", "advanced maternal age", and "high body mass index (BMI)". Relevant retrospective studies, cohort studies, and meta-analyses were included if clinical outcomes, such as the number of oocytes retrieved, embryo quality, pregnancy rates, or live birth rates, were reported. Studies were selected based on relevance, methodological clarity, and focus on specific patient subgroups. A systematic review was conducted to identify relevant studies on PPOS published in the past 10 years, focusing on English-language articles with significant data or new insights. Initially, 60 articles were screened from academic databases, of which 43 were selected after reviewing titles, abstracts, and keywords. Most articles were from the last 5 years, reflecting recent advancements, while some older studies on the physiological aspects or pioneering use of PPOS in ovarian stimulation were also included for their foundational contributions. The final 43 articles met the quality and relevance criteria for the review.

2.1 Definition, Classification, and Mechanism of Action of Progestins in PPOS Protocols

Progestins comprise a broad group of steroid compounds that exhibit biological activity similar to that of natural progesterone. In addition to endogenous progesterone, produced primarily by the corpus luteum and placenta, and to a lesser extent by the adrenal glands, various synthetic progestins have been developed. The essential feature of all progestins is their ability to bind to progesterone receptors (PRs) [1,12].

Progestins are classified into several categories based on chemical structure:

- Retroprogesterones: Structurally closest to natural progesterone.
- Pregnane derivatives: These include MPA and cyproterone acetate. MPA is a synthetic progestin with high progestational activity and potent anti-gonadotropic action, widely used in PPOS protocols [1,13].
- Norpregnane derivatives—nomegestrol acetate.
- 19-nortestosterone derivatives: Includes estranes (e.g., norethindrone, norethisterone acetate) and gonanes (e.g., norgestrel, levonorgestrel).
- Spironolactone derivatives—drospirenone [14].
- Other compounds: Additional compounds used in various ovarian stimulation contexts include micronized progesterone, dydrogesterone (DYG), and desogestrel [1].

According to Ata *et al*. [1], progestins differ in potency to inhibit ovulation. This variability is summarized in the following Table 1 (Ref. [1]):

Table 1. Comparison of progestins based on the dose required to inhibit ovulation [1].

Progestin	Ovulation inhibition dose (mg/day)
Progesterone	300
Dydrogesterone	>30
Medroxyprogesterone acetate	10
Cyproterone acetate	1
Nomegestrol acetate	5
Norethisterone acetate	0.5
Levonorgestrel	0.05
Drospirenone	2

Progestins bind to progesterone receptors in two isoforms: PR-A, associated with inhibitory functions, and PR-B, linked to stimulatory activity [12]. Although all progestins bind to these receptors, the chemical structures, receptor affinities, and antigonadotropic potencies of these isoforms differ significantly [1,14].

These pharmacodynamic differences are clinically relevant. For example, MPA exhibits potent suppression of gonadotropin release, allowing effective inhibition of the LH surge at relatively low doses. In contrast, natural or micronized progesterone requires much higher doses to achieve the same effect [14]. Consequently, some progestins may offer more stable hypothalamic-pituitary suppression, while others may have broader spectra of safety profiles or different side effects.

Therefore, the choice of progestin in PPOS protocols should be guided not only by the route of administration and availability but also by each compound's pharmacological characteristics, relative potency, and expected clinical outcomes. Current evidence confirms that while all progestins used in PPOS can suppress the LH surge, the required doses and the intensity of suppression vary considerably among molecules [1,14].

The mechanism of action of progestins involves the inhibition of endogenous gonadotropin secretion, particularly LH, via negative feedback on the hypothalamic-pituitary axis, as we could see on Fig. 1. This modulation allows more precise control of follicular development and prevents premature LH surges that could trigger spontaneous ovulation [6].

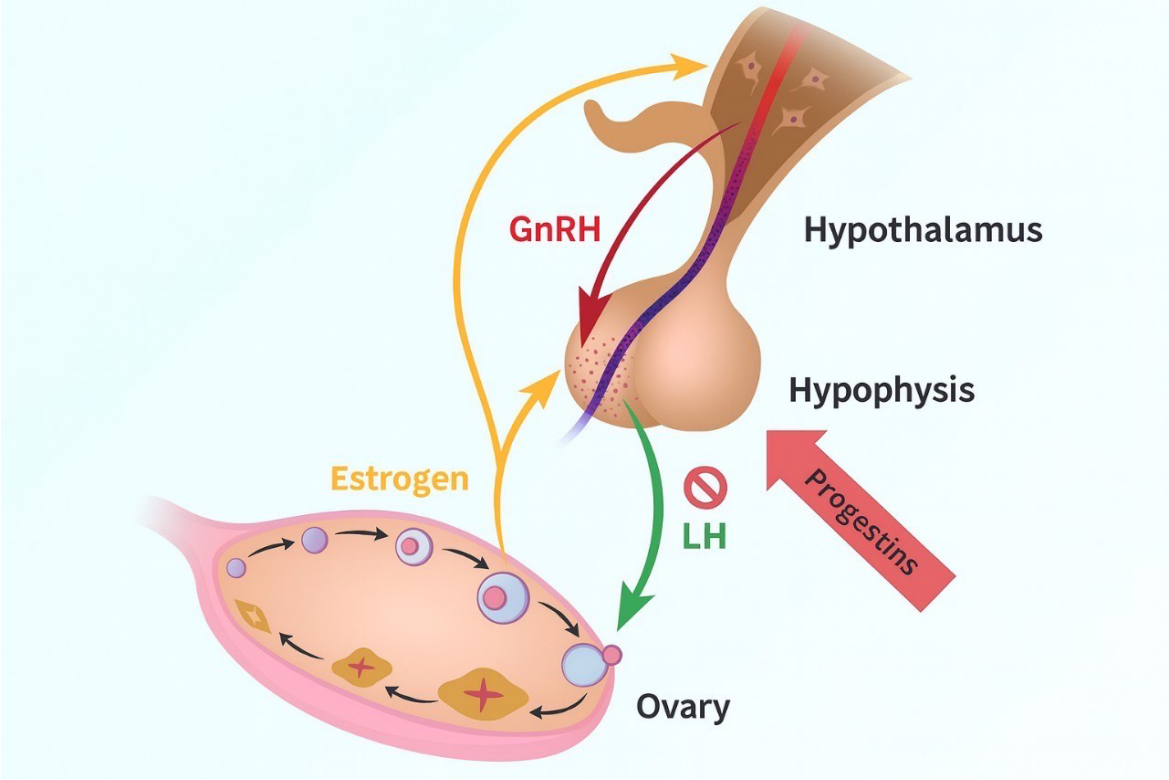

Fig. 1. Hypothalamo-hypophysial gonadal axis and the process through which the luteinizing hormone (LH) peak is inhibited after progestin administration. GnRH, gonadotropin-releasing hormone. The Figure created with CANVA.

- LH suppression:

Progestogens block the pulsatile release of GnRH in the hypothalamus, reducing pituitary stimulation and, thus, endogenous LH and follicle-stimulating hormone (FSH) secretion [1].

- Follicular development control:

By inhibiting endogenous gonadotropins, PPOS allows follicular growth to be controlled exclusively by exogenous gonadotropins administered during treatment.

- Flexibility in treatment initiation:

PPOS allows ovarian stimulation to be initiated at any time during the menstrual cycle without waiting for a specific phase [15].

2.2 Types of PPOS Protocol

There are two protocols through which progestins can be administered (Fig. 2).

1. Fixed protocol: Progestins (such as MPA) and gonadotropins are administered simultaneously from the beginning of the early follicular phase and maintained until the day of final oocyte maturation induction [16,17].
2. Flexible PPOS protocol: Progestin administration begins when the leading follicle reaches a size of 12–14 mm or when serum estradiol levels exceed 200–400 pg/mL, usually around day 7 of stimulation [16,17].

The flexible PPOS protocol aims to reduce progestin exposure during the early phase of follicular development without compromising LH peak suppression.

Several studies have analyzed the efficacy and outcomes of both protocols:

- Retrospective studies have shown that both protocols with PPOS flexible and fixed are equally effective in preventing premature LH surges in patients with diminished ovarian reserve, with no difference in fertilization rates, clinical pregnancy rates, or the number of MII oocytes obtained [13,18].
- Giles *et al.* [17] emphasized that both the fixed and flexible protocols are equally safe and effective, with no significant differences in reproductive outcomes [17].

While both PPOS schemes are currently considered valid, cPPOS is the most widely used in clinical practice.

2.3 Advantages and Disadvantages of Using PPOS

The PPOS protocol with progestins has been consolidated as an effective alternative to traditional protocols based on GnRH agonists or antagonists. The use of the PPOS protocol has demonstrated multiple benefits, including preventing premature LH surge, providing greater

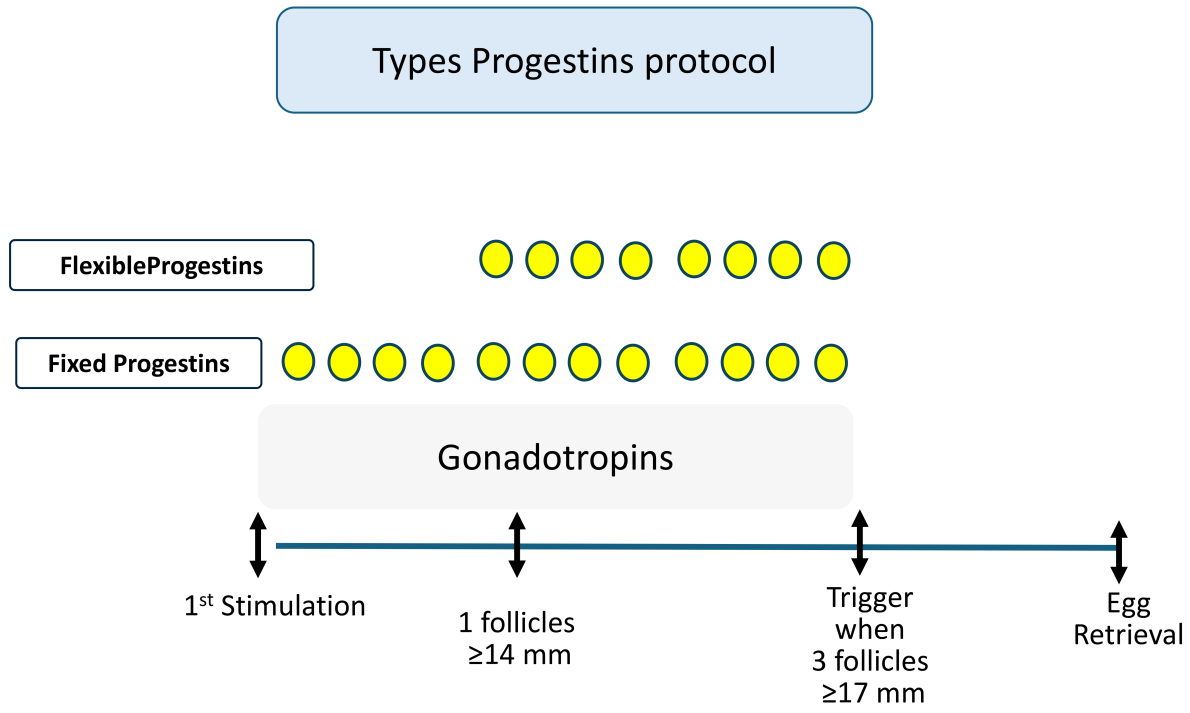

Fig. 2. Types of progestin-primed ovarian stimulation (PPOS) protocols.

patient comfort through oral administration, and reducing costs, especially in delayed transfer cycles. However, this approach also has significant limitations, including the inability to perform fresh transfers, a longer total treatment duration, and limited evidence in specific clinical subgroups.

Table 2 (Ref. [1–4,8,10,16,17,19,20,42]) presents a comparative summary of the main advantages and disadvantages of the PPOS protocol, and the associated references.

3. Clinical Applications of the PPOS Protocol in Various Assisted Reproduction Patient Populations

This article reviews studies on the clinical applications of the PPOS protocol across various patient populations, examining the efficacy and safety of the protocol compared with conventional GnRH antagonist or agonist protocols in cycles without planned fresh embryo transfer.

3.1 Egg Donation

Three key studies have compared PPOS with conventional antagonist protocols in oocyte donation.

Beguería *et al.* [10] conducted a controlled trial and found that the number of retrieved mature oocytes was similar between the MPA and antagonist groups. However, pregnancy and ongoing pregnancy rates in recipients were significantly lower in the MPA group. Although the recipients were not randomized—a limitation in interpreting the findings—the authors suggested that oocyte competence may have been compromised in the MPA group [10]. Ultimately, the limited sample size in the study and the mixing of transfers on days 3 and 5 compromise the robustness of the findings.

In contrast, one year later, Giles *et al.* [17] published a prospective, randomized controlled trial demonstrating that MPA use yielded outcomes comparable to those of the antagonist protocol for the number of oocytes retrieved and for pregnancy and live birth rates in recipients. The discrepancy with the findings of Beguería *et al.* [10] is likely attributable to differences in study design, particularly in embryo transfer practices (blastocyst vs. cleavage stage transfers) [17]. These results align with additional evidence supporting the notion that PPOS yields outcomes similar to those of GnRH antagonist protocols.

Further supporting the safety of PPOS, Devesa *et al.* [21] evaluated the use of PPOS in oocyte donors receiving desogestrel (DSG) and analyzed outcomes in recipients of vitrified oocytes.

Devesa *et al.* [21] observed no significant differences in fertilization rates, embryo development, or live birth rates, reinforcing that PPOS does not adversely affect oocyte quality or recipient outcomes in oocyte cryopreservation [21].

Table 3 (Ref. [10,17,21]) summarizes the most relevant clinical studies investigating PPOS in women undergoing egg donation.

Table 2. Comparison of the advantages and disadvantages of the PPOS protocol in ovarian stimulation.

Advantages	Disadvantages
Effective prevention of premature LH surge and early luteinization [3,17].	Requires a 'freeze-all' strategy as the protocol compromises endometrial receptivity [1,8].
Oral administration, greater convenience for the patient [2,4].	Longer time to pregnancy due to the need for delayed transfer [16].
Lower initial treatment cost [3].	Potentially higher cumulative cost per live birth due to cryopreservation and delayed transfer [19].
Reduced risk of OHSS in PCOS [4,10].	Limited evidence on side effects and patient satisfaction [1].
Reduced gonadotropin dose and duration in normal responders [2].	Optimal progestogen, dose, and administration route have not been defined [17].
Comparable clinical results in women with normal ovarian reserve [3,20].	Overexpression of mitochondrial genes related to oxidative phosphorylation, suggesting potential mitochondrial involvement in reduced oocyte quality. Future studies should be conducted to investigate this with different types of progesterone [42].

PCOS, polycystic ovary syndrome; OHSS, ovarian hyperstimulation syndrome.

- PPOS yields reproductive outcomes in oocyte donation comparable to those of conventional protocols.
- PPOS promotes convenience for oral administration, potential cost reductions, and applicability in strategies such as oocyte vitrification or random initiation of stimulation.
- Although short-term results are favorable, further studies are required to evaluate neonatal outcomes and long-term safety.

The evidence suggests that the PPOS protocol effectively obtains mature oocytes from donors. Reproductive outcomes are comparable to standard protocols, especially when embryos are vitrified. The clinical context, center logistics, and donor convenience should be considered when choosing a protocol.

Once the efficacy of the protocol was demonstrated in oocyte donors, PPOS was introduced in fertility preservation cycles.

3.2 Fertility Preservation

PPOS has proven to be an effective and safe strategy for fertility preservation. Table 4 (Ref. [22–24]) summarizes the major studies in both medical and non-medical preservation.

- PPOS is a safe and effective option for fertility preservation in oncological and endometriosis settings. Moreover, PPOS allows random-start stimulation, which is essential for patients with urgent medical needs. Protocols with dienogest yielded similar results to those of conventional protocols and exhibited good tolerance. PPOS can facilitate clinical logistics without compromising efficacy.
- In particular, if a fresh embryo transfer is planned or occurs in women with progesterone receptor-positive tumors, caution should be exercised for which administration is not recommended [10,11].

3.3 Endometriosis

Progesterone is known to help treat endometriosis; thus, for these patients, fertility preservation through oocyte vitrification is recommended. It is worth mentioning a retrospective, multicenter study that evaluated whether the PPOS protocol with dienogest is similar to protocols with GnRH agonists and antagonists, allowing hormonal treatment to be maintained during ovarian stimulation without compromising efficacy [25]. In this study, 201 stimulation cycles were performed in 130 women with endometriosis, and the three protocols were compared. The PPOS protocol with dienogest was non-inferior in the number of mature oocytes retrieved and exhibited a similar tolerance and safety profile. This strategy allows continuity of treatment for endometriosis, with lower cost and oral administration. Yang *et al*. [26] retrospective cohort study of 605 infertile women with endometrioma undergoing IVF/ICSI-ET compared the PPOS, ultra-long GnRHa, and GnRH antagonist protocols, finding that PPOS resulted in lower biochemical, clinical pregnancy, and live birth rates than the ultra-long GnRHa protocol, but similar outcomes to the GnRH antagonist protocol.

Table 5 compares the various stimulation protocols used for fertility preservation in patients with endometriosis.

The use of dienogest in the PPOS protocol is effective and safe. Indeed, dienogest in the PPOS protocol facilitates the continuity of endometriosis treatment and represents an accessible and convenient alternative to preserve fertility in these patients.

3.4 Preimplantation Genetic Testing (PGT)

Patients designated for PGT undergo deferred transfer, which is why using the PPOS protocol is an option. The possible impact of the protocol on embryo euploidy and clinical outcomes after euploid embryo transfer represents a growing area of interest.

Table 3. Relevant clinical studies on PPOS in oocyte donation.

Study	Type of study	Progestagen	Control (antagonist)	Donor results	Results in receivers	Final comment
Beguería *et al.* (2019) [10]	Prospective RCT	MPA 10 mg/day	Ganirelix 0.25 mg/day	Number oocytes MII similar	Lower pregnancy and ongoing pregnancy rates with MPA	No randomization of recipients. Possible effect on oocyte.
Devesa *et al.* (2022) [21]	Retrospective, cohort	DSG 75 µg/day	Ganirelix 0.25 mg/day	Comparable results	Similar live birth rate in vitrified oocytes	PPOS valid in vitrification and fertility preservation.
Giles *et al.* (2024) [17]	Prospective (donor), retrospective (recipient) RCT	MPA 10 mg/day	Ganirelix 0.25 mg/day	Equivalent outcomes (number MTII, duration, FSH)	Similar pregnancy and live birth rates between groups	Reinforces the viability of PPOS as a convenient alternative.

RCT, randomized controlled trial; MPA, medroxyprogesterone acetate; DSG, desogestrel; MII, metaphase II; FSH, follicle-stimulating hormone; MTII, mature oocytes at Metaphase II.

Table 4. Comparison between ovarian stimulation protocols for fertility preservation.

Study/author	Type of study	Population	Comparison/design	Key findings
Mathieu d'Argent *et al.* (2020) [22]	Retrospective cohort	108 women with endometriosis	PPOS vs. GnRH-antagonist	Comparable FP results between protocols
Iwami *et al.* (2021) [23]	Prospective	150 women with endometriosis	PPOS with dienogest vs. didrogesterone	New strategy; both safe and effective
Filippi *et al.* (2023) [24]	Comparative	124 women with cancer	PPOS in an oncological context	PPOS is effective in young oncologic women; viable option in FP

FP, fertility preservation.

Table 5. Comparison of ovarian stimulation protocols for fertility preservation in endometriosis.

Variable	PPOS + dienogest	GnRH antagonist	GnRH agonist
Mature oocytes (mean)	Not inferior	Reference	Reference
Continuity of treatment with dienogest	Yes	No	No
Route of administration	Oral	Injectable	Injectable
Estimated cost	Low	High	High
Total gonadotropin dose	Similar	Similar	Similar
Complications (OHSS, infections)	Low, no difference	Low, no difference	Low, no difference
Reported tolerance	Good	Good	Good
Stimulation duration	Variable, similar to the antagonist	Variable	Longer

The reviewed studies compared the PPOS protocol with the GnRH antagonist protocol with respect to euploidy rates, laboratory results, and clinical outcomes.

- Pai *et al*. [27] conducted a retrospective cohort study involving 128 cycles with PGT-A. In the overall population, Pai and co-authors observed a significantly lower euploidy rate per biopsied blastocyst in the PPOS group (26.8%) versus the GnRH-ant group (33.0%) ($p = 0.029$). This difference was more significant in women aged 38 years or older, with a rate of 5.4% in the PPOS group versus 26.7% in the GnRH-ant group ($p = 0.006$); however, clinical outcomes after euploid embryo transfer were comparable between groups.
- Giles *et al.* [28] conducted a multicenter, retrospective, observational cohort study demonstrating that, in PGT-A cycles, MPA was as effective as GnRH antagonists in terms of the number of mature oocytes obtained, the rate of embryo development, and the rate of ongoing pregnancies. Notably, MPA was associated with a lower clinical miscarriage rate and fewer aneuploid or mosaic blastocysts. Although gonadotropin use was higher with MPA, the protocol offered logistical and psychological benefits, making MPA a patient-friendly alternative for pituitary suppression when a fresh embryo transfer is not planned.
- Vidal *et al*. [29] conducted a prospective, crossover study involving 44 patients aged 38 years or older, comparing the two protocols in sequential cycles within the same patient. Although PPOS produced more oocytes and MII oocytes, there was no significant difference in the mean number of euploid embryos per patient. Euploidy rates were similar (29% in PPOS vs. 35% in GnRH-ant), but the difference was not statistically significant. This suggests that, when controlling for individual variables, PPOS does not compromise the euploidy rate in older patients.
- Qin *et al*. [30] combined a retrospective cohort study with 962 cycles and a meta-analysis of seven primary studies. Qin and co-authors found no significant differences in stimulation parameters, euploidy rates, or clinical outcomes between PPOS and GnRH-ant protocols. However, the meta-analysis revealed a significantly lower miscarriage rate with PPOS (odds ratio (OR) = 0.67; $p = 0.02$), suggesting an additional benefit.
- Li *et al.* [31] published the protocol of an ongoing randomized controlled trial designed to compare the rate of blastocyst euploidy between PPOS (using dydrogesterone) and GnRH-ant in women undergoing PGT-A. The study included 400 participants and represents a significant effort to generate high-quality evidence in this area.

Recent high-level evidence, including a large randomized controlled trial comparing PPOS with GnRH antagonist protocols in PGT-A cycles, demonstrated no difference in blastocyst euploidy rates, total and euploid blastocyst yields, or live birth outcomes following frozen embryo transfer [30]; however, miscarriage rates were significantly lower with PPOS. These results were corroborated by a retrospective cohort and meta-analysis encompassing 962 cycles [31], which similarly found comparable embryonic and pregnancy outcomes between PPOS and traditional GnRH-based protocols.

Earlier retrospective studies (e.g., Pai *et al.* [27]) suggesting reduced euploidy in older patients undergoing PPOS have not been confirmed by these recent, methodologically stronger investigations and should be interpreted with caution due to small sample sizes and design limitations.

Overall, current data support the use of PPOS as a patient-friendly alternative, particularly in well-supported clinical scenarios where a fresh embryo transfer is not planned (e.g., fertility preservation and PGT-A cycles). However, well-powered randomized controlled trials across diverse populations are still needed to further validate long-term safety and efficacy, especially in subgroups such as poor responders or endometriosis patients.

3.5 Polycystic Ovary Syndrome (PCOS)

A recent meta-analysis evaluated the efficacy and safety of the PPOS protocol in women with PCOS undergoing IVF/ICSI. Nine studies (three randomized controlled trials and six cohort studies), with a total of 2289 patients, comparing PPOS with GnRH agonist and antagonist protocols were included [32]. The main results of the meta-analysis are summarized in Table 6.

PPOS has not demonstrated superiority over conventional protocols in terms of live birth rates or prevention of OHSS. However, PPOS remains an effective and safe alternative, particularly attractive for women with PCOS when combined with a freeze-all strategy. Nevertheless, the current evidence is limited by the small number of randomized controlled trials and the high heterogeneity across available studies. PPOS is suitable for freezing at all stages in patients with PCOS, but high doses of gonadotropin need to be carefully balanced.

Reviewing the studies in terms of the ovarian response of the patients, the main findings were:

3.6 Low Ovarian Response

Several studies have assessed the efficacy of the PPOS protocol in patients with a low ovarian response. However, outcomes vary depending on the criteria used to define the low response (e.g., POSEIDON vs. Bologna).

- Zhang *et al*. [33] conducted a retrospective cohort study comparing cumulative live birth rates (CLBRs) between the GnRH antagonist and PPOS regimens in patients with low prognosis, as defined by the POSEIDON criteria. The study found that GnRH antagonists were associated with significantly higher CLBRs, especially in older women ($\geq$35 years) with low ovarian reserve

Table 6. Main results of the Yang meta-analysis.

Variable analyzed	PPOS vs. GnRH analogues	Certainty of evidence
Premature LH peak	No cases reported in any of the groups	Moderate
Total gonadotropin dose	Significantly higher in PPOS	Moderate
Number of mature oocytes (MII)	Similar between both protocols	Low
Live birth rate (LBR)	No significant difference	Low
Incidence of moderate or severe OHSS	No significant difference	Low
Total number of oocytes recovered	Comparable	Low
Good quality embryos	No differences	Low
Implantation rate (IR)	Tendency to be higher in PPOS (cohort studies)	Low
Clinical pregnancy rate (CPR)	Tendency to be higher in PPOS (vs. agonist)	Low
Ongoing pregnancy rate (OPR)	Similar to protocol with antagonist	Low

(Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number (POSEIDON) group 4).

- Guan *et al*. [34] conducted a meta-analysis of randomized controlled trials evaluating the efficacy of PPOS in patients with varying ovarian reserves, including those with diminished ovarian reserve (DOR). In the DOR subgroup, two studies showed significantly higher numbers of retrieved oocytes and viable embryos in the PPOS group. Although LH levels on the trigger day were lower for PPOS, this difference was not statistically significant. The overall conclusion was that PPOS is an effective stimulation protocol for patients across different levels of ovarian reserve.
- Zhao and Wang [35] compared PPOS with minimal stimulation using clomiphene citrate (CC) plus gonadotropins in women aged $\geq$35 years, classified as group 4 using POSEIDON. PPOS effectively suppressed premature LH surges and significantly increased the proportion of mature (MII) oocytes. However, there were no significant differences in total oocyte yield, fertilization rate, number of day-3 good-quality embryos, transferable embryos, or frozen blastocysts. The study concluded that PPOS is a feasible option in this subgroup.

PPOS effectively prevents premature LH surges and improves oocyte maturation, particularly in advanced maternal age patients with poor ovarian response (POSEIDON group 4). Meta-analytic data suggest improved oocyte and embryo outcomes in low responders, as defined by the Bologna criteria. However, one study indicated that GnRH antagonists may offer superior CLBR in older patients with POSEIDON group 4, highlighting the need for more standardized comparative studies.

It is important to consider the heterogeneity of both protocols and their impact on the reported outcomes. PPOS improves the low response outcome defined by Bologna, but GnRH antagonists may be superior in the POSEIDON group.

3.7 High Ovarian Response

Chen *et al*. [36] compared PPOS and GnRH antagonist protocols in women undergoing their first IVF cycle with a high expected ovarian response (AFC $>$15). Both medroxyprogesterone acetate and dydrogesterone effectively suppressed the LH surge. LH peaks ($\geq$10 IU/L) were rare and similar between groups (0.5% in PPOS vs. 0% in antagonists). Due to the endometrial impact of progestins, all embryos in the PPOS group required elective freezing. Nonetheless, clinical outcomes (live birth, clinical pregnancy, miscarriage, neonatal complications) were comparable between protocols. Importantly, no moderate or severe cases of OHSS were reported, confirming the safety of the PPOS strategy with freeze-all and GnRH agonist triggering.

Table 7 (Ref. [33–36]) summarizes key studies that are divided according to ovarian response.

4. Neonatal Safety and Risk

The safety of dydrogesterone during early pregnancy remains a subject of ongoing debate, particularly concerning the potential link to congenital anomalies such as hypospadias and congenital heart defects (CHDs). Recent literature presents conflicting findings, drawing from pharmacovigilance reports, meta-analyses, and observational cohort studies.

Henry *et al*. [37] conducted a disproportionality analysis using the World Health Organization (WHO) global safety database (VigiBase) and reported that dydrogesterone was associated with a significantly increased reporting odds ratio (ROR) for congenital anomalies (ROR, 6.0 vs. ART drugs; ROR, 5.4 vs. progesterone). The most frequently reported anomalies were hypospadias (32%) and CHDs (27%). Although the authors acknowledged limitations such as underreporting and indication bias, the authors emphasized that these findings represented a potential safety signal warranting further investigation.

However, this interpretation has subsequently been challenged. Pabuccu *et al*. [38] offered a critical appraisal, arguing that the overall birth malformation reporting rate (~0.7%) was markedly lower than the expected ART-associated rate (~6%), suggesting potential underreporting. Furthermore, Pabuccu and co-authors questioned the reliability of ROR calculations, mainly when based on small case-to-non-case ratios, and highlighted the lack of strong biological plausibility for a teratogenic effect.

Table 7. Summary table of key studies by ovarian response subgroup.

Study	Population	Comparison	Key findings	Conclusion
Zhang *et al*. (2021) [33]	POSEIDON low prognosis (esp. group 4)	PPOS vs. GnRH antagonist	Higher CLBR in the antagonist group	GnRH antagonist superior in older low responders
Guan *et al*. (2021) [34]	DOR (meta-analysis)	PPOS vs. various controls	↑ oocytes and embryos in PPOS; NS difference in LH	PPOS effective across ovarian reserve profiles
Zhao and Wang (2023) [35]	POSEIDON group 4 (≥35 years)	PPOS vs. minimal stim (CC + Gn)	↑ MII oocytes with PPOS; no other significant differences	PPOS feasible for advanced age low responders
Chen *et al*. (2024) [36]	High responders (AFC >15)	PPOS vs. GnRH antagonist	Comparable clinical outcomes; low LH surge; no OHSS	PPOS safe and effective with freeze-all strategy

CLBR, cumulative live birth rates; DOR, diminished ovarian reserve; CC, clomiphene citrate; Gn, gonadotropins; AFC, antral follicular count; NS, No Significative; ↑, increase in number.

Therefore, these authors urged caution in interpreting pharmacovigilance data, particularly given the widespread clinical use and cultural relevance of dydrogesterone as an oral progestin.

In addition to these pharmacovigilance findings and critiques, observational and meta-analytic studies have provided further insights. For instance, Huang *et al*. [39] conducted a retrospective cohort study in China involving 3556 live births following IVF with vitrified embryo transfer. Even after adjusting for potential confounders, Huang and co-authors found no significant differences in congenital malformation rates between the dydrogesterone-exposed group (1.12%) and the GnRH agonist protocol group (1.08%).

Similarly, Katalinic *et al*. (2024) [40] conducted a systematic review and meta-analysis that included nine studies, comprising both randomized controlled trials and observational designs, totaling 2680 live births. The analysis yielded a pooled risk ratio for congenital anomalies of 0.92 in randomized controlled trials and 1.11 in low-bias observational studies, neither of which reached statistical significance. Moreover, the overall anomaly rate (2.5%) was consistent with the EUROCAT baseline prevalence. Nevertheless, the authors acknowledged several limitations, such as small sample sizes, the rarity of outcomes, and inconsistent reporting standards across studies.

Thus, the current evidence regarding the teratogenic potential of dydrogesterone remains inconclusive. While pharmacovigilance data suggest a possible safety signal, observational and meta-analytic research findings have not confirmed a statistically significant risk. These discrepancies likely reflect inherent methodological differences, data limitations, and variability in reporting practices, underscoring the need for further well-designed, prospective studies to provide definitive clarification of the risk profile of dydrogesterone in early pregnancy. Moreover, we cannot overlook that these studies focus on neonatal safety in patients who use dydrogesterone during the luteal phase and not during the ovarian stimulation phase of a cycle in which no embryo transfer will occur.

5. Role of LH in PPOS Cycles?

A retrospective, observational study [41] analyzed the evolution of LH levels during the follicular phase in controlled ovarian stimulation (COS) cycles, comparing six protocols that combined different GnRH analogs (antagonist, long agonist, and short agonist) with gonadotropins (human menopausal gonadotropin (hMG) or recombinant FSH) in more than 2200 ART cycles. The results showed significant differences in LH evolution across protocols. In particular, cycles with antagonists showed a significant daily decrease in LH, more pronounced with rec-FSH than with hMG, possibly due to the LH activity present in hMG. Although prior use of oral contraceptives (OCPs) reduced basal and mean LH levels, OCPs did not affect the evolution of LH levels throughout the cycle. No significant changes in LH were observed in the long agonist protocols, and a slight increase was recorded in the short agonist protocols with hMG [42].

These findings underscore the importance of understanding how LH varies across stimulation protocols and raise concerns about possible LH depletion in cycles with antagonists, especially rec-FSH, which may sometimes warrant LH supplementation. Future studies should include PPOS to assess whether LH evolution in these cycles behaves similarly to that observed with antagonists and whether some patient groups under PPOS might benefit from the addition of LH.

6. New Findings and Future Research

A recent retrospective Japanese study [42] compared the PPOS protocol using chlormadinone acetate with the GnRH antagonist protocol using cetrorelix in women under 40 with usual ovarian reserve undergoing IVF with a freeze-all strategy. While the PPOS protocol effectively suppressed premature LH surges, this protocol was associated with significantly lower rates of ongoing pregnancy, implantation, and live birth after the first frozen embryo transfer, despite no differences in oocyte retrieval or fertilization rates.

Additionally, the PPOS group showed a lower proportion of good-quality embryos on day 3. Notably, molecu-

lar analysis of mural granulosa cells using single-cell RNA sequencing revealed an overexpression of mitochondrial genes involved in oxidative phosphorylation. This suggests a possible mitochondrial contribution to the reduced oocyte quality observed with PPOS. These findings indicate that, although PPOS effectively prevents premature LH surges, PPOS may negatively influence oocyte quality and reproductive outcomes in normal-ovulatory patients.

7. Conclusions

PPOS has proven to be a safe and effective therapeutic option in multiple clinical settings. The advantages of PPOS include ease of oral administration, lower cost, and adequate control of the hypothalamic-pituitary-gonadal axis. However, the use of PPOS is limited to cycles requiring mandatory embryo vitrification, as this protocol suppresses the receptive endometrium.

In populations such as those with low ovarian response or patients with PCOS, PPOS is positioned as a handy tool to maximize oocyte recovery and avoid cancellations. In oocyte donation, the logistics and economic benefits make the PPOS protocol attractive without sacrificing efficacy. In cases of endometriosis or fertility preservation, the protocol provides clinical flexibility without compromising results.

Future research should prioritize randomized controlled trials evaluating the effect of different progestogens (e.g., progesterone versus medroxyprogesterone acetate) on oocyte quality, as well as studies assessing alternative PPOS strategies in patients with progesterone receptor-positive tumors. In addition, further investigation into the role of mitochondrial function in oocyte development is warranted. Finally, comprehensive cost-effectiveness analyses, particularly considering the cumulative costs of frozen embryo transfer cycles, would provide valuable insights for optimizing clinical decision-making.

The PPOS protocol represents a valid, non-inferior alternative to GnRH antagonists in various clinical populations when an oocyte or embryo-freezing strategy is employed. The application of the PPOS protocol should be individualized according to the characteristics of the patient and the therapeutic goals of the cycle. Nonetheless, PPOS represents an effective alternative at present, owing to the safe and comfortable nature of the protocol for patients. However, we must continue to investigate the use of other progestogens, alongside the associated efficacy and safety.

Author Contributions

MC, IPZ and EG designed the research study. MC and IPZ performed the research. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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