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*Original Research*

# Progestin-Primed Ovarian Stimulation with Dydrogesterone Improves Oocyte and Embryo Outcomes in Women Undergoing *In Vitro* Fertilization: A Randomized Controlled Study

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**Abstract**

**Background**: Progestin-primed ovarian stimulation (PPOS) using dydrogesterone (DYG) has emerged as a potential alternative to conventional gonadotropin-releasing hormone antagonist (GnRH-ant) protocols for controlled ovarian stimulation (COS) cycles. However, the efficacy of the DYG-based PPOS regimen has not been well established. This study aimed to assess the efficacy and safety of the DYG-based PPOS protocol compared to the conventional GnRH-ant regimen during the various stages of COS and intra-cytoplasmic sperm injection (ICSI) procedures. **Methods**: A randomized controlled trial (RCT) was conducted on 200 infertile women who underwent COS using either the GnRH-ant (n = 100) or PPOS (n = 100) protocols. Generalized linear regression analysis with the appropriate distribution was applied to estimate the adjusted effect of the PPOS protocol on oocyte maturation and retrieval, fertilization, and embryo formation. **Results**: Both treatment groups had comparable hormonal profiles and procedural characteristics. Compared to the GnRH-ant protocol, the PPOS protocol resulted in an average increase of 1.67 oocytes per retrieval (95% confidence interval (CI): 0.29; 3.04; $p = 0.017$). The PPOS protocol demonstrated a modest yet significant improvement in the likelihood of oocyte maturation, with an adjusted mean difference of 4.2% (95% CI: 0.4; 8.0; $p = 0.03$), corresponding to an odds ratio of 1.23 (95% CI: 1.02; 1.47; $p = 0.03$). The fertilization and embryo development rates (cleavage embryos and blastocysts) were similar between the two protocols. **Conclusions**: Our findings suggest that the PPOS protocol using DYG offers a slight yet significant advantage over the GnRH-ant protocol regarding the total number of retrieved oocytes and the maturation rate, while maintaining comparable fertilization rates and embryo development outcomes. **Clinical Trial Registration**: The study has been registered on https://classic.clinicaltrials.gov/ (registration number: NCT06191809).

**Keywords:** controlled ovarian stimulation; GnRH antagonist protocol; progestin-primed ovarian stimulation (PPOS)

## 1. Introduction

Controlled ovarian stimulation (COS) is a crucial step in assisted reproductive technology (ART), and premature luteinizing hormone (LH) surge is the leading cause of cycle cancelation during COS [1].

The progestin-primed ovarian stimulation (PPOS) protocol was introduced by Kuang *et al.* [2] in 2015, with medroxyprogesterone acetate (MPA) used as an inhibitor of the LH surge. The underlying mechanism utilizes the properties of progesterone to reduce the pulsatility of gonadotropin-releasing hormone (GnRH) antagonists within the hypothalamus, thereby effectively suppressing the typical rise in LH levels triggered by increasing estradiol. It has been demonstrated that the outcomes of the PPOS protocol with MPA are comparable to those of the short GnRH antagonist (GnRH-ant) protocol [2]. Those findings have established a new trend in ART research.

Unlike the GnRH-ant and GnRH agonist protocols, the PPOS protocol offers potential advantages, including lower costs and greater convenience through oral administration [3]. The only drawback of the PPOS protocol is that premature exposure of the endometrium to progesterone during the cycle may lead to asynchronous endometrial development [4].

Further research data indicate that the PPOS protocol with MPA produced similar outcomes to GnRH-ant cycles in terms of premature ovulation, oocyte quality, and rates of implantation, as well as live births or ongoing pregnancies, in patients with and without PCOS [5,6]. Later, Martínez *et al.* [7] demonstrated that inhibition of early LH peaks could be effectively achieved using desogestrel (DSG) instead of MPA, and that the outcomes in terms of the quantity of retrieved oocytes or the clinical pregnancy rate were also comparable to the GnRH-ant protocol. More recently,

dydrogesterone (DYG) has emerged as a promising alternative due to its high selectivity and potent progestogenic activity, specifically targeting progesterone receptors [8]. Unlike other progestins, DYG does not demonstrate clinically significant agonistic or antagonistic effects on androgen, estrogen, or glucocorticoid receptors, and possesses only mild antimineralocorticoid properties. Additionally, DYG distinguishes itself from natural progesterone through its enhanced oral bioavailability, which may contribute to a reduced incidence of progestin-associated side effects [8,9]. Recent evidence also suggests that MPA, a potent LH inhibitor, may excessively suppress pituitary function during ovarian stimulation. This suppression is significantly greater compared to the weaker LH inhibition observed with DYG [10]. This excessive LH suppression with MPA is concerning, as it may negatively impact oocyte and embryo outcomes. Conversely, the milder LH-lowering effects of DYG might better preserve endogenous LH levels, which are essential for optimal follicular growth and development. Therefore, DYG's balanced LH modulation could reduce the risk of premature LH surges while supporting oocyte and embryo quality, making it a viable alternative to both MPA and DSG. To date, only a few studies have evaluated the effectiveness of the DYG-based PPOS protocol [10,11]. Preliminary findings indicate that this protocol effectively suppresses the premature LH surge and shows non-inferior clinical pregnancy outcomes compared to the GnRH antagonist protocol. However, more extensive data are still required to thoroughly evaluate the effectiveness of the DYG-based PPOS regimen across successive stages of COS and intracytoplasmic sperm injection (ICSI) procedures. To address this knowledge gap, we conducted a randomized controlled study to evaluate the safety and effectiveness of the PPOS protocol using DYG against the standard GnRH-ant protocol. Our primary outcomes included the number of retrieved oocytes, the maturation rate, and the fertilization and embryo development success rates.

## 2. Materials and Methods

### *2.1 Study Design*

This open-label, prospective randomized controlled trial (registration number: NCT06191809) was conducted at the Assisted Reproduction Center of Tam Anh General Hospital between February 2023 and January 2024. The study was approved by the Institutional Ethical Review Board of Hanoi Medical University (decision number: 842; reference IRB-VN01.001/IRB00003121/FWA 00004148).

The primary objective of this study was to evaluate the efficacy of the PPOS protocol in comparison with the control group, which received a GnRH-ant protocol. All participants were informed of the study details and provided informed consent before participation.

Our clinical trial included: (1) infertile women aged between 20 and 45 years, regardless of their ovarian reserve status; (2) those who were undergoing ICSI in a single cycle and planning to use either the GnRH-ant protocol or the PPOS protocol; and (3) voluntary agreement to participate in the study.

Participants were excluded from the study based on the following criteria: (1) presenting contraindications to ovarian stimulation and ICSI treatment; (2) having systemic diseases such as kidney failure, lupus erythematosus, and depression, hyperprolactinemia or other endocrine disorders; (3) using hormonal drugs within the past three months; (4) having an abnormal uterine cavity structure, endometriosis or cancer; (5) undergoing random-start cycles; oocyte donation cycles or (6) embryo biopsy.

### *2.2 Sample Size Consideration*

The sample size determination process is detailed in the **Supplementary Materials**. In brief, the study sample size was estimated to optimize the precision of the non-inferiority statistical inference through a Negative Binomial (NBI) regression model, which aims to compare the average number of retrieved oocytes (or metaphase II (MII) oocytes) between two distinct groups, as described by Cundill and Alexander (2015) [12]. The estimation formula accounted for the mean and dispersion of outcomes in both groups, an expected statistical power of 80%, a significance threshold of 0.05, and a non-inferiority margin of 1.5 units.

A simulation process was conducted using the retrospective data from 804 patients who underwent ovarian stimulation at Tam Anh General Hospital during the period between August and December 2023. The results (**Supplementary Fig. 1**) indicated that a sample comprising 200 patients (equally split between groups) would be required. This size ensured a precise statistical inference for the number of retrieved or MII oocytes between the PPOS and control groups with a statistical power of 80%, and a non-inferiority margin would not exceed 1.5 units.

### *2.3 Randomization Process*

A stratified randomization process was applied to ensure the unbiased allocation of participants to the GnRH-ant and PPOS treatment arms. Detailed descriptions can be found in the **Supplementary Materials**. In brief, each participant was categorized based on the "patient-oriented strategies encompassing individualized oocyte number (POSEIDON)" criterion, a categorical stratification variable with four potential categories: P1, P2, P3, and P4. They were allocated to these strata by a predefined probability distribution of 14.86%, 25.39%, 15.99%, and 43.76%, respectively, as derived from the actual distribution of POSEIDON categories among patients who underwent *in vitro* fertilization (IVF) treatment at Assisted Reproduction Center of Tam Anh General Hospital between 2020 and 2022. Within each "POSEIDON" stratum, the participants were equally randomized across the two treatment groups (GnRH-ant or PPOS protocol).

### *2.4 COS and ICSI protocols*

#### 2.4.1 Ovarian Stimulation Protocols

The ovarian stimulation protocols have been described in previous studies [13,14] and are detailed in the study protocol (online **Supplementary Materials**). In brief, COS was initiated on the second day of menstruation, using a recombinant follicle-stimulating hormone (Follitrope, LG Chem, Seoul, Republic of Korea) with doses ranging from 150 to 300 international units (IU) administered daily. The initial gonadotropin dosage was determined based on the patient's clinical profiles and was subsequently titrated based on the folliculogenesis response.

In the control group, pituitary suppression was started on stimulation day six with the administration of 0.25 milligrams of GnRH-ant (Ganirelix, Orgalutran, Vetter Pharma-Fertigung GmbH & Co. KG, Ravensburg, Germany) or Cetrorelix (Cetrotide, Merck Healthcare KGaA, Darmstad, Germany). In the progestin-primed ovarian stimulation (PPOS) group, 30 mg/day of dydrogesterone was administered from cycle day two until trigger day. It is noteworthy that the daily dose of DYG in PPOS protocols varied across studies, ranging from 20 mg to 40 mg [15]. We selected a dose of 30 mg/day based on prior evidence demonstrating its effectiveness in preventing premature LH surges while maintaining a favorable safety profile [16].

Serum estradiol ($E_2$) and progesterone (P4) levels were measured on stimulation day two and the trigger day. The serum LH level was measured on stimulation days 2, 6, and 8 and the trigger day, using a competitive electrochemiluminescence immunoassay with a Cobas analyzer (Cobas Pro, Roche-Hitachi, Rotkreuz, Switzerland).

Final oocyte maturation was induced once the dominant follicles reached $\geq$20 mm in diameter or at least three follicles met the 18 mm threshold. To mitigate the risk of ovarian hyperstimulation, 0.2 mg Triptorelin (Diphereline, Ipsen Pharma Biotech, Boulogne-Billancourt, France) alone was administered to high-risk patients, and a dual trigger consisting of 2000 IU human chorionic gonadotropin (hCG) (IVF-C, LG Chem, Seoul, Republic of Korea) combined with 0.2 mg Triptorelin (Diphereline, Ipsen Pharma Biotech, France) was used for the remaining patients.

#### 2.4.2 Oocyte Retrieval

Oocyte retrieval via transvaginal aspiration was performed 35–36 h after final oocyte maturation. Following the standard procedure at the hospital, oocyte–cumulus complexes were incubated in G-IVF medium (Vitrolife, Gothenburg, Sweden) using Origio benchtop incubators (Origio, Trumbull, CT, USA) (for two hours to promote nuclear maturation [13,14]. After the cumulus cells were removed, the denuded oocytes were examined under an inverted microscope to verify their MII status. Oocytes that were degenerate, large, or severely dysmorphic were considered unsuitable.

#### 2.4.3 ICSI Protocol

The ICSI procedure was performed by embryologists 3–4 h after retrieval. The resulting zygotes were cultured in a continuous single medium (Fujifilm Irvine Scientific, Santa Ana, CA, USA) in incubators with 37 °C, 5% $O_2$, and 6% $CO_2$ until day 3. Embryologists applied strict morphological criteria to retain only the normally fertilized two-pronuclei zygotes and to eliminate abnormal multinuclear embryos. Cleavage-stage quality was assessed based on cell number, fragmentation, multinucleation, and uniformity at 67–69 h per the Istanbul consensus.

#### 2.4.4 Embryo Development

On post-ICSI day 3, after speaking with an embryologist, the couple was asked whether they wished to continue growing their embryos until the blastocyst stage or opt for cryopreservation. For those patients who opted for continued growth, the quality of the resulting blastocysts was then evaluated. To evaluate the quality of blastocysts, the embryologists applied the Gardner and Schoolcraft classification system, which considers the embryo development stage, trophoblast morphology, and inner cell mass morphology. The blastocysts were then graded as AA, AB, BA, or BB, indicating exceptional quality. Poor-quality embryos were blastocysts classified as AC, CA, BC, CB, or CC [17].

### *2.5 Statistical Analysis*

Data analysis and visualization were performed using the R programming language (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria). To verify the effectiveness of randomization, the distribution characteristics of baseline parameters in each group were described using medians and 5th–95th percentiles range for quantitative variables and percentages for categorical factors. Difference between the two groups was assessed using the Mann-Whitney U test for quantitative variables and the $\chi^2$ or Fisher's exact test for categorical variables. The following analytical procedure was applied to evaluate multiple outcomes across successive stages of controlled ovarian stimulation.

Count data, such as the number of retrieved and mature oocytes and the number of embryos, were described using medians and 5th–95th percentiles. The adjusted effect of the PPOS protocol on these outcomes was assessed through regression analysis using a generalized linear model (GLM) with a Negative Binomial (NBI) distribution. The suitability of the NBI distribution for the dataset was rigorously validated, with results presented in the supplemental data (**Supplementary Fig. 2**).

Success rates, including maturation rate, fertilization rate, probabilities of achieving day 3 and day 5 embryos, and their transferability, were also summarized using medians and 5th–95th percentiles. The effectiveness of the PPOS protocol compared to the GnRH-ant protocol in terms

of success rates was evaluated by adjusted risk differences (aRD) and adjusted odds-ratio (aOR) derived from a binomial regression model.

NBI and binomial regression models were fitted using the GAMLSS package (version 5.4-22, https://cran.r-project.org/web/packages/gamlss/index.html) [18]. To achieve a precise estimation of the effect of the PPOS protocol, adjustments for baseline and procedural factors [maternal age, antral follicle count (AFC), baseline levels of anti-Müllerian hormone (AMH) and LH, trigger method, total follicle-stimulating hormone (FSH) dose, and length of stimulation] were implemented within the regression analysis framework. The plausibility of the adjusted factors was confirmed through least absolute shrinkage and selection operator (LASSO) regression variable selection. Confidence intervals (CI) for marginal effects were calculated using the delta method [19]. Statistical inferences were based on 95% CI and null hypothesis testing at a significance level of 0.05.

## 3. Results

### *3.1 Study Population Characteristics*

The present study involved 200 infertile women who were randomized and assigned to either the GnRH-ant protocol (n = 100) or the PPOS protocol (n = 100). The flowchart for the study is shown in Fig. 1.

As shown in Table 1, there were no significant differences in the baseline characteristics between the two groups. The study population consisted of a general population of infertile women aged between 25 and 38 years, with various causes of infertility and differing ovarian responses. The basal levels of LH, FSH, estradiol, and progesterone were not significantly different between the two groups. It is worth noting that the distribution of crucial factors such as AFC and AMH was well balanced across the two treatment arms, ensuring the reliability of the randomization process.

### *3.2 Technical Profile and Dynamics of the Ovarian Stimulation Cycle*

A summary of the procedural aspects of the ovarian stimulation cycle for each protocol is presented in Table 2. The PPOS protocol had a marginally shorter duration than the GnRH-ant group, although the difference was not statistically significant. The total FSH dose was similar in both protocols, with an average value of approximately 2700 IU. The hormonal profiles on the trigger day were consistent, indicating a comparable physiological response for both stimulation protocols. This consistency extended to the distribution of other factors, including the trigger method and sperm retrieval technique, confirming the technical uniformity across both protocols.

A specific monitoring process was carried out to track the evolution of LH levels across six time points (days 2, 6, and 8 and the trigger day) in the PPOS protocol group. The results of pair-wise comparison are presented in the online **Supplementary Materials** (**Supplementary Table 1**). In brief, the data showed a progressive and significant reduction in LH levels during the cycle under the PPOS protocol (–14.83% at day 6, –31.07% at day 8, and –46.24% at trigger day), achieving a median level of 3.18 mIU/mL at the trigger day (Fig. 2).

The PPOS and GnRH-ant protocols achieved satisfactory overall success, with only 1% and 2% cancelation rates, respectively (not statistically significant). Notably, only one instance of slight ovarian hyperstimulation was observed in each group.

### *3.3 Effectiveness of the PPOS Protocol on the Primary Outcomes*

Our primary study aimed to compare the effectiveness of the PPOS protocol with that of the GnRH-ant protocol across various stages of the IVF process, such as oocyte maturation and retrieval, fertilization, and embryo formation. The outcomes were evaluated at each stage in terms of the absolute quantity and probability of success. A descriptive analysis of these outcomes can be found in the Supplementary Materials (**Supplementary Tables 2,3**). Additionally, regression analysis was performed to estimate the adjusted effects of the PPOS protocol on the quantitative outcomes and probability of success.

#### 3.3.1 Oocyte Retrieval

The median number of oocytes retrieved was higher in the PPOS group than in the GnRH-ant group (13.5 *vs.* 11) (**Supplementary Table 2**). Further analysis using NBI regression indicated a modest but significant benefit of the PPOS protocol regarding the number of oocytes retrieved, with an adjusted mean improvement of 1.67 oocytes (95% CI: 0.29; 3.04; $p = 0.017$) (Table 3).

#### 3.3.2 Oocyte Maturation

The PPOS protocol showed a marginal improvement compared to the GnRH-ant group in the number of MII oocytes (median values: 9 *vs.* 8 oocytes) and maturation rate (73.34% *vs.* 70.03%). NBI regression analysis indicated a slight but significant adjusted effect of 1.46 mature oocytes (95% CI: 0.28; 2.64; $p = 0.016$), favoring the PPOS protocol (Table 3). Binomial regression analysis with adjustment revealed that applying the PPOS protocol increased the likelihood of maturation by an average of 4.2% (95% CI: 0.4; 8.0; $p = 0.03$) (Table 4), corresponding with an OR of 1.23 (95% CI: 1.02; 1.47) (**Supplementary Table 4**).

#### 3.3.3 Fertilization Rate

The fertilization rates after ICSI showed no significant differences between the two protocols. The adjusted difference in the success rate based on binomial regression was minimal (aRD = 1.8%, 95% CI: –1.7; 5.2; $p = 0.312$ and

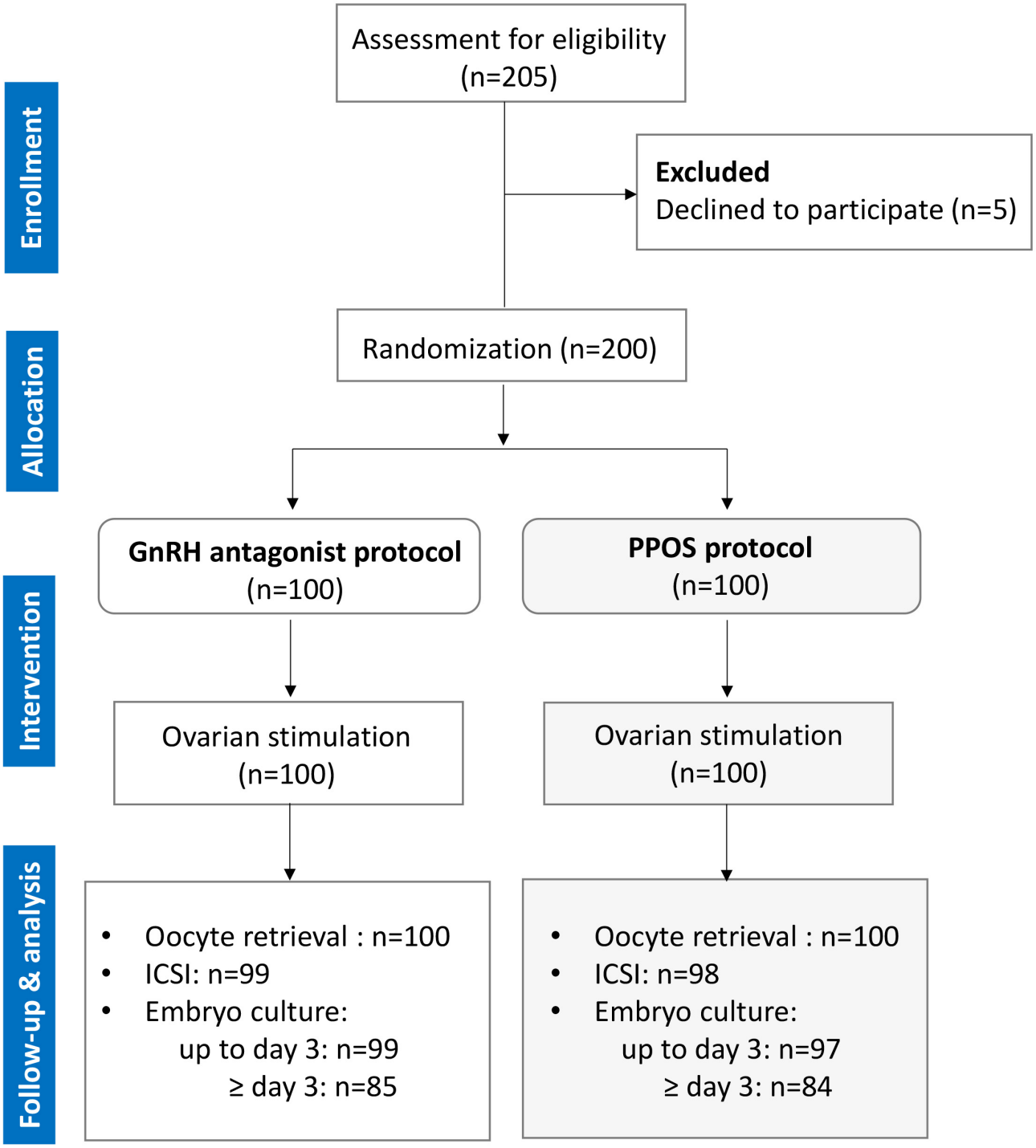


**Fig. 1. Flowchart of the study**. PPOS, progestin-primed ovarian stimulation protocol; ICSI, intra-cytoplasmic sperm injection; GnRH, gonadotropin-releasing hormone.

aOR = 1.15; 95% CI: 0.88; 1.51; $p$ = 0.315), indicating a comparable chance of fertilization success between the oocytes retrieved from the two protocols (**Supplementary Tables 3,4**).

3.3.4 Embryo Development

The NBI regression analysis on count data (Table 3) showed a quantitative advantage of the PPOS protocol over GnRH-ant, with a significant increase in the number of cleavage embryos (adjusted effect = 1.36, 95% CI: 0.30; 2.42; $p$ = 0.012) and good blastocysts (adjusted effect = 0.62, 95% CI: 0.05; 1.20; $p$ = 0.033). However, the findings regarding the probability of a successful formation of cleavage embryos and blastocysts did not show a significant superiority of the PPOS protocol (Table 4).

**Table 1. Characteristics of the study population.**

| Parameters | GnRH-ant (n = 100) | | PPOS (n = 100) | | Statistic* | *p*-value# |
|---|---|---|---|---|---|---|
| Numerical | Median | 5th–95th percentiles | Median | 5th–95th percentiles | | |
| Maternal age (years) | 31.0 | 25.0–38.0 | 30.0 | 25.0–37.0 | 0.343 | 0.731 |
| Paternal age (years) | 33.0 | 28.0–43.0 | 34.0 | 27.0–47.2 | –0.325 | 0.745 |
| BMI (kg/m$^2$) | 21.5 | 17.3–27.1 | 20.9 | 18.3–26.1 | 1.460 | 0.144 |
| Infertility duration (year) | 3.0 | 1.0–10.0 | 3.0 | 0.5–9.0 | 0.639 | 0.522 |
| AFC (follicles) | 16.0 | 4.0–42.4 | 16.0 | 6.0–42.0 | –0.439 | 0.661 |
| AMH (ng/mL) | 2.73 | 0.68–8.01 | 2.65 | 0.55–9.23 | –0.310 | 0.757 |
| Endocrine profiles | | | | | | |
| LH (mIU/mL) | 5.83 | 2.64–11.17 | 5.65 | 3.07–13.03 | –0.783 | 0.434 |
| FSH (mIU/mL) | 6.63 | 4.10–10.64 | 6.33 | 4.25–9.04 | 1.167 | 0.243 |
| Estradiol (mIU/mL) | 35.54 | 15.67–65.72 | 34.83 | 18.63–74.83 | –0.301 | 0.763 |
| Progesterone (mIU/mL) | 0.22 | 0.05–0.59 | 0.21 | 0.05–0.52 | –0.188 | 0.851 |
| Categorical | | | | | | |
| Maternal age <35 years (%) | | 84 | | 82 | 0.035 | 0.851 |
| Maternal age ≥35 years (%) | | 16 | | 18 | | |
| Infertility type | | | | | | |
| Primary (%) | | 56 | | 56 | 0.000 | 1.000 |
| Secondary (%) | | 44 | | 44 | | |
| Infertility diagnosis | | | | | | |
| Tubal (%) | | 10 | | 16 | 1.105 | 0.293 |
| Ovulatory dysfunction (%) | | 15 | | 8 | 1.769 | 0.183 |
| Endometriosis (%) | | 1 | | 0 | N/A | 1.000 |
| Mono-factor (female) (%) | | 20 | | 13 | 1.306 | 0.253 |
| Multi-factor (female) (%) | | 9 | | 13 | 0.460 | 0.498 |
| Male factors (%) | | 11 | | 12 | 0.000 | 1.000 |
| Unexplained (%) | | 32 | | 34 | 0.023 | 0.880 |
| Previous IVF attempts | | | | | | |
| 0 cycle (%) | | 75 | | 78 | 0.111 | 0.739 |
| 1–2 cycle (%) | | 22 | | 19 | 0.123 | 0.726 |
| >2 cycles (%) | | 3 | | 3 | N/A | 1.000 |
| Previous retrieved oocytes | | | | | | |
| Null (%) | | 75 | | 78 | 0.111 | 0.739 |
| ≥1 (%) | | 25 | | 22 | | |
| POSEIDON category | | | | | | |
| NOR (%) | | 78 | | 76 | 0.028 | 0.866 |
| Class I–II (%) | | 4 | | 3 | N/A | 1.000 |
| Class III (%) | | 12 | | 14 | 0.044 | 0.833 |
| Class IV (%) | | 6 | | 7 | 0.000 | 1.000 |

Note: BMI, body mass index; AFC, antral follicle count; AMH, anti-Müllerian hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; POSEIDON, patient-oriented strategies encompassing individualized oocyte number; NOR, normal ovarian response; IVF, *in vitro* fertilization; GnRH-ant, gonadotropin-releasing hormone antagonist; PPOS, progestin-primed ovarian stimulation; N/A, not applicable. *: Z values based on U statistics in Mann-Whitney U test for numerical data, or $\chi^2$ statistic for categorical data; #: *p*-values were based on the Mann-Whitney U test for numerical data (under the null hypothesis that the distribution of those variables is the same across the two treatment groups), and $\chi^2$ or Fisher's exact tests for categorical variables (under the null hypothesis that the distribution of these variables is independent of the treatment groups).

A similar analysis evaluating the advantages of the PPOS protocol over GnRH-ant in terms of success probabilities in COS-ICSI procedure, expressed as an odds ratio, yielded consistent results. These findings are presented in **Supplementary Table 3** of the supplemental document.

Fig. 3 shows the overall effectiveness of the PPOS protocol across the five phases in the IVF funnel compared to that of the GnRH-ant protocol. This visualization indicates that the PPOS protocol may offer a significant advantage in the quantitative outcomes of oocyte retrieval

**Table 2. Technical profile of ovarian stimulation cycle.**

| Parameters | GnRH-ant (n = 100) | | PPOS (n = 100) | | Statistic* | *p*-value# |
|---|---|---|---|---|---|---|
| Numerical | Median | 5th–95th percentiles | Median | 5th–95th percentiles | | |
| Length of stimulation (days) | 10.00 | 8.95–11.00 | 10.00 | 8.00–11.00 | 1.986 | 0.047 |
| Total FSH dose (IU) | 2700 | 2025–3000 | 2700 | 1642.5–3000 | 1.158 | 0.247 |
| Length of antagonist (days) | 5.00 | 3.95–6.00 | - | - | - | - |
| LH level at day 6 (mIU/mL) | - | - | 5.42 | 2.36–10.47 | - | - |
| LH level at day 8 (mIU/mL) | - | - | 3.89 | 1.77–10.31 | - | - |
| LH level at trigger day (mIU/mL)* | - | - | 3.18 | 0.85–8.10 | - | - |
| Estradiol level at trigger day (mIU/mL) | 3084 | 1193.7–9032.65 | 3391 | 1258.35–10,430 | –0.780 | 0.435 |
| P4 level at trigger day (mIU/mL) | 1.05 | 0.37–3.77 | 1.15 | 0.13–3.09 | –0.576 | 0.565 |
| Categorical parameters | | | | | | |
| Trigger methods | | | | | | |
| GnRH Agonist trigger (%) | | 32 | | 36 | 0.200 | 0.654 |
| Dual trigger (%) | | 68 | | 64 | | |
| Source of sperms (%) | | | | | | |
| From donation (%) | | 1 | | 1 | | |
| Ejaculation (%) | | 97 | | 91 | N/A | 0.045 |
| mTESE (%) | | 2 | | 2 | | |
| PESA (%) | | - | | 6 | | |

Note: FSH, follicle-stimulating hormone; LH, luteinizing hormone; P4, progesterone; GnRH, gonadotropin hormone-releasing hormone; mTESE, microscopic testicular sperm extraction; PESA, percutaneous epididymal sperm aspiration; N/A, not applicable. For numerical data: *: Z values based on U statistics in Mann-Whitney U test; #: *p*-value was based on the Mann-Whitney U test to verify whether the distribution of a variable is similar between two treatment groups. For categorical data: *: value of $\chi^2$ statistic; #: *p*-value was based on $\chi^2$ or Fisher's exact tests under the null hypothesis that the distribution of that variable is independent of the treatment groups.

and oocyte maturation and equivalent performance to the GnRH-ant protocol regarding fertilization and embryo development.

## 4. Discussion

The primary finding of our research is that the PPOS protocol with DYG resulted in a noticeable improvement in the quantity of oocyte retrieval and maturation rate while maintaining equivalent performance in fertilization rate and embryo development outcomes, as compared to the GnRH-ant protocol.

Recently, several advancements in vitrification technology have broadened the scope of IVF practices. One such innovation is the incorporation of progestins as alternatives to GnRH-ant to prevent premature LH surges during controlled ovarian stimulation. This has resulted in the development of a new protocol known as the PPOS protocol [20]. Among the various available progestins, DYG is particularly noteworthy because of its close resemblance to endogenous progesterone. This offers a patient-centered approach with several advantages, including the convenience of oral administration, minimal androgenic effects, a reduced incidence of adverse reactions, and a strong affinity for the progesterone receptor [21].

Although the efficacy of the PPOS regimen has been examined in several previous studies, our study had several notable strengths. To the best of our knowledge, our study is the first to implement an randomized controlled trial (RCT) design with a well-organized randomization process and standardized COS-ICSI procedure in both treatment arms to determine the efficacy of the PPOS protocol. In addition, the use of an advanced regression analysis framework enabled a comprehensive evaluation of the treatment effect of the PPOS protocol for both quantitative endpoints and the likelihood of achieving successful outcomes at each stage of the COS-ICSI process, surpassing traditional analysis methods. We also visualized for the first time the beneficial impact of the PPOS protocol on consecutive outcomes across the IVF process (known as the "IVF funnel"), potentially leading to an increased overall success rate. Finally, our study findings apply to a general population of infertile Asian women, signifying a significant improvement in generalizability compared to previous studies that primarily focused on specific cohorts such as oocyte donors or individuals with diminished ovarian reserves.

There are several similarities between our study and that of Hossein Rashidi *et al.* [22], which also employed DYG (20 mg/day) on a comparable sample size. They also achieved better outcomes in terms of retrieved oocytes, maturation rate, and good-quality embryos compared to the GnRH-ant protocol. However, their clinical trial focused exclusively on normal ovarian responders, whereas our study targeted a general population of infertile women.

**Table 3. Effect of PPOS protocol on quantitative outcome.**

| Outcome (number) | Unadjusted effect (PPOS–GnRH-ant) | | | Adjusted effect (PPOS–GnRH-ant) | | |
|---|---|---|---|---|---|---|
| | Estimated | 95% CI | *p*-value | Estimated | 95% CI | *p*-value |
| 12–13 mm follicles on trigger-day | −0.10 | −0.74; 0.53 | 0.749 | −0.50 | −1.21; 0.23 | 0.178 |
| 14–24 mm follicles on trigger-day | 1.26 | −0.53; 3.04 | 0.167 | 1.44 | 0.44; 2.44 | 0.005 |
| Retrieved oocytes | 1.19 | −0.92; 3.31 | 0.269 | 1.67 | 0.29; 3.04 | 0.017 |
| MII oocytes | 1.10 | −0.58; 2.77 | 0.200 | 1.46 | 0.28; 2.64 | 0.016 |
| Cleavage embryos | 0.93 | −0.57; 2.43 | 0.223 | 1.36 | 0.30; 2.42 | 0.012 |
| Good cleavage embryos | 0.49 | −0.61; 1.60 | 0.380 | 0.51 | −0.40; 1.42 | 0.269 |
| Blastocytes | 0.59 | −0.60; 1.77 | 0.332 | 0.87 | −0.01; 1.74 | 0.052 |
| Good blastocytes | 0.40 | −0.35; 1.14 | 0.298 | 0.62 | 0.05; 1.20 | 0.033 |

Note: these marginal effects measure the average oocyte or embryo count difference between the PPOS and GnRH-ant protocols using negative binomial regression analysis. A positive marginal effect value suggested that PPOS was superior to GnRH-ant. Two models were used for each outcome: an unadjusted model considering only the protocol type and an adjusted model including maternal age, trigger method, AFC, AMH, basal LH level, and total FSH dose as covariates. Statistical testing was performed to determine whether the marginal effects differed significantly from zero at a significance threshold of 0.05. CI, confidence intervals; MII, metaphase II.

**Table 4. Effect of PPOS protocol on the probabilities of success.**

| Probabilities of success | Unadjusted risk difference (PPOS–GnRH-ant) | | | Adjusted risk difference (PPOS–GnRH-ant) | | |
|---|---|---|---|---|---|---|
| | Estimated | 95% CI | *p*-value | Estimated | 95% CI | *p*-value * |
| Maturation | 0.019 | −0.017; 0.054 | 0.301 | 0.042 | 0.004; 0.080 | 0.030 |
| Fertilization | 0.016 | −0.017; 0.048 | 0.344 | 0.018 | −0.017; 0.052 | 0.312 |
| Cleavage embryos | 0.005 | −0.029; 0.039 | 0.771 | 0.016 | −0.021; 0.053 | 0.391 |
| Good cleavage embryos | −0.010 | −0.055; 0.036 | 0.671 | 0.021 | −0.028; 0.070 | 0.392 |
| Blastocytes | −0.023 | −0.074; 0.028 | 0.379 | 0.003 | −0.052; 0.058 | 0.925 |
| Good blastocytes | −0.001 | −0.051; 0.049 | 0.981 | 0.023 | −0.031; 0.077 | 0.402 |

Note: risk differences (RD) quantify the difference in the likelihood of achieving a desired outcome per oocyte/embryo unit between the PPOS and GnRH-ant protocols across a set of oocytes/embryos undergoing specific procedures (e.g., MII oocyte retrieval, ICSI fertilization, and embryo culture). A positive RD suggests the superiority of the PPOS protocol over the GnRH-ant protocol. Unadjusted RD was estimated using a univariate binomial model, with only the PPOS/GnRH-ant protocol type as a predictor. Adjusted effect estimations employed a binomial model incorporating covariates such as maternal age, trigger method, AFC, AMH level, basal LH levels, and total FSH dose. **p*-values were derived from statistical testing to verify whether the RD was null at a significance threshold of 0.05.

A systematic review and meta-analysis of PPOS and GnRH-ant protocols found comparable outcomes regarding ovarian stimulation response, gonadotropin consumption, the number of retrieved oocytes, and MII oocytes [23]. Several studies have investigated the effectiveness of PPOS in patients with PCOS, but the results are inconsistent due to differences in the study design, dosage, and type of progestin used [23,24].

Only three RCT studies have been conducted. One of these compared the effectiveness of PPOS with DYG and GnRH-ant in a specific cohort of women with PCOS [23], while the other two studies used MPA [25,26]. A subsequent study found no significant differences in the number of retrieved oocytes, the maturation rate, the fertilization rate, the cleavage embryos, the production of viable embryos, or the cycle cancelation rate between the two groups [13]. However, the major limitation of that study was the use of alternating allocation instead of a true randomization process, which did not allow for the complete control of potential confounding factors.

The PPOS protocol helps to maintain sensitivity in the pituitary gland, which allows for the administration of gonadotropin releasing hormone agonist (GnRHa) to stimulate ovulation. However, relying solely on GnRHa can lead to an inadequate response from the hypothalamic–pituitary–ovarian axis (LH levels $\leq$15 IU/L), which is associated with a lower oocyte retrieval rate [27]. Previous studies have demonstrated that a dual-trigger strategy, combining GnRHa with a small dose of hCG, can effectively overcome this limitation without increasing the risk of ovarian hyperstimulation syndrome (OHSS) [27]. In this study, we utilized both trigger methods: either 0.2 mg of triptorelin

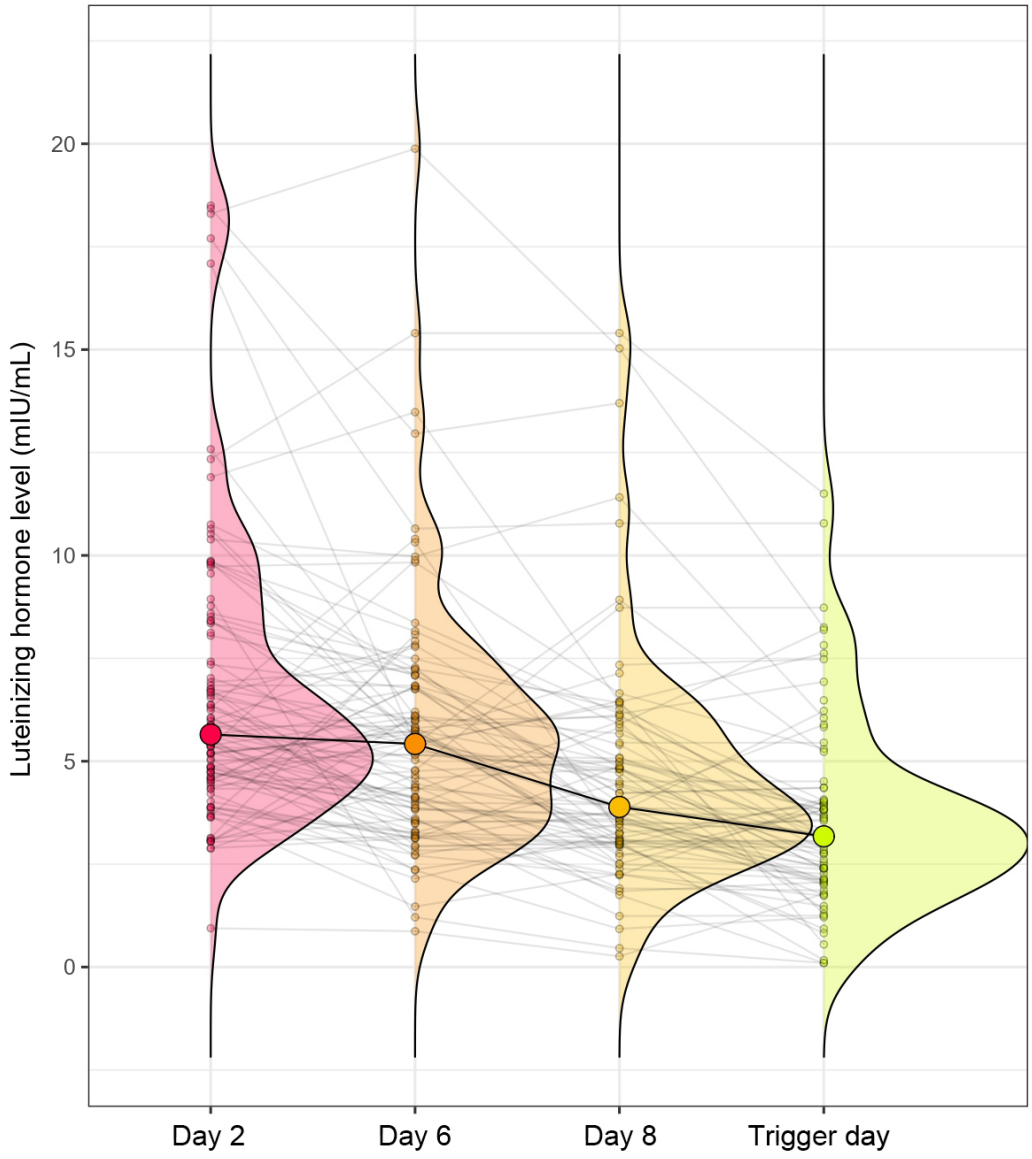


**Fig. 2. Evolution of the luteinizing hormone level in the PPOS group**. The graph illustrates the progression of luteinizing hormone (LH) levels from the commencement of menstruation to the initiation of ovulation stimulation for every subject in the PPOS regimen cohort. Measurements were taken on day 2, the first day of the menstrual cycle, and on days 6 and 8, corresponding to days 6 and 8. The 'trigger day' represents the day at which ovum maturation is initiated.

alone or a dual trigger comprising 2000 IU of hCG and 0.2 mg of triptorelin [27,28].

Regarding the dosage of DYG in the PPOS protocol, previous research has lacked uniformity in the daily doses administered. As a result, there is no consensus on the minimum effective dose of DYG required to suppress the hypothalamic-pituitary axis. In a recent systemic review, a minimum daily dose of 30 mg of DYG was found to be necessary to inhibit ovulation consistently [29]. Prior studies have used DYG doses of 20 or 30 mg/day [13,23,24]. However, one study suggested that 30 mg/day was necessary for the effective suppression of ovulation [13]. Interestingly, the ORCHIDEA study found that DYG prescribed at 20–30 mg/day for endometriosis patients was associated with five spontaneous pregnancies, indicating that the LH surge may not be fully controlled at these doses [30]. Therefore, our study chose a daily DYG dose of 30 mg to ensure effective LH suppression.

The current study may be hindered by the lack of data on embryo transfer and pregnancy outcomes, including implantation rates, ongoing pregnancies, live birth rates, and the long-term safety of children conceived through PPOS using DYG. Our study did not include a detailed cost-effectiveness analysis, which would require considering factors such as the costs of thawed embryo transfers.

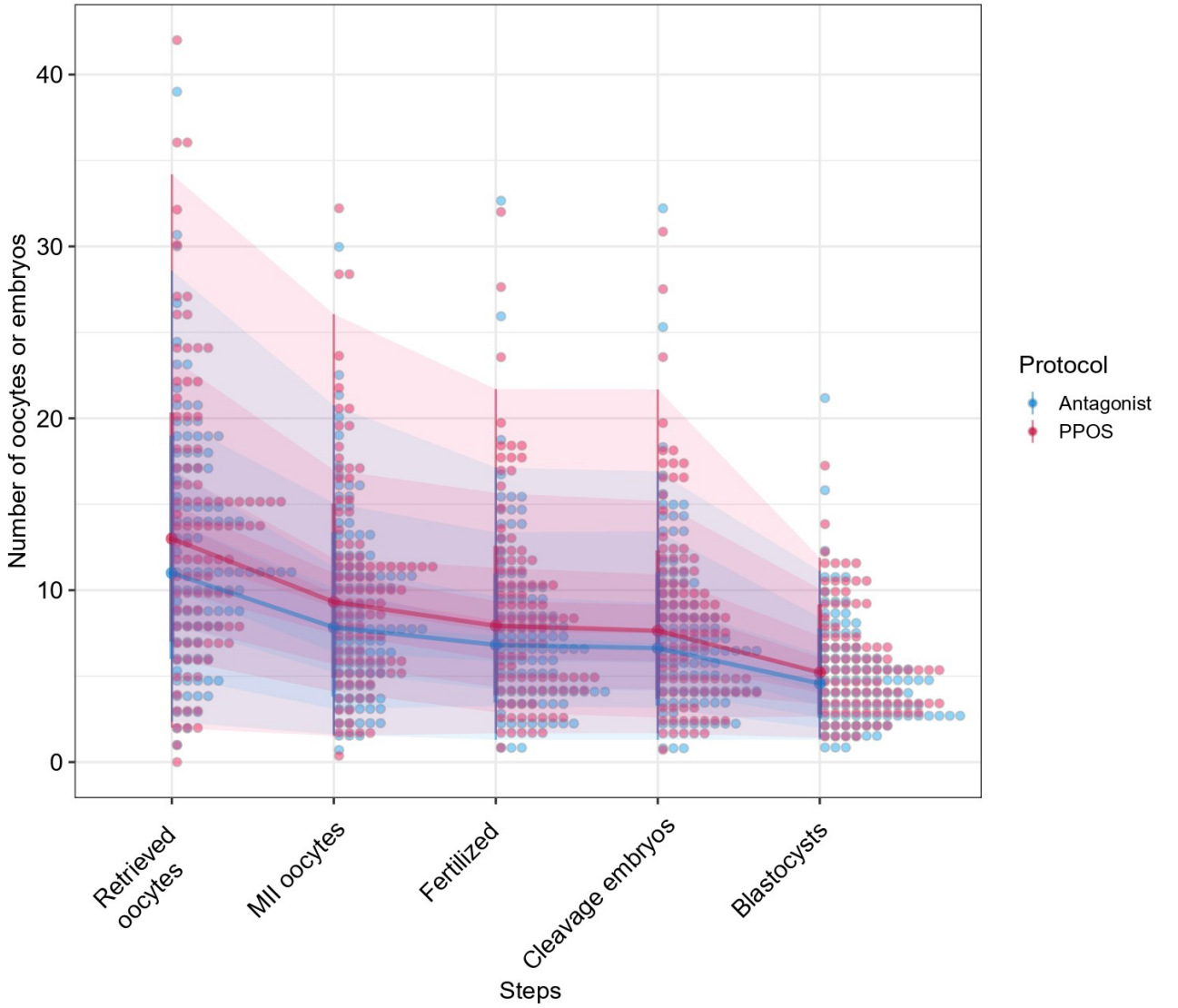


**Fig. 3. Overall effectiveness of PPOS versus GnRH-ant protocol in the IVF funnel**. The figure consists of two layers; in the background, a dot plot represents the distribution of oocytes/embryo quantity (Y-axis) across five successive stages in the IVF funnel (X-axis). The data were based on the true observed quantity of oocytes retrieved, and the individual probability of success was estimated using four binomial regression models. Each dot represents an individual observation point. Multiple color bands indicate the 5th, 25th, 75th, and 95th percentiles of the outcomes. The front layer consists of line and point-range plots showing the primary outcomes' trend and distribution characteristics. The larger dots indicate the median value at each stage, and the bold line connecting these dots indicates the outcome trend. Blue indicates the GnRH-ant protocol for all graphic elements, and pink indicates the PPOS protocol.

Nevertheless, limiting the follow-up to the fertilization and embryo outcomes would not significantly impact the conclusion regarding the efficacy of PPOS treatment. Early outcomes, including ovarian responses and fertilization rate, are reasonable, given the mechanism of the intervention. Choosing intermediate outcomes may reduce the required sample size and accelerate the validation of the efficacy or failure of a new intervention [31]. In addition, extending the scope of evaluation may be unnecessary if there is no expectation of superiority in later outcomes. Indeed, previous studies have consistently shown that the PPOS regimen showed only equivalent efficacy for ongoing pregnancy and live birth rates, while findings on neonatal outcomes remain inconclusive, indicating the need for further research in this area. Our findings reveal that, following fertilization, there was no statistically significant difference between the PPOS and GnRH-ant protocols regarding the likelihood of obtaining transferable embryos. However, the advantage of the PPOS protocol in enhancing primary outcomes, specifically the production of more retrieved and mature (MII) oocytes, could potentially improve the overall success rate of the IVF procedure [32].

DYG is widely prescribed for the prevention of threatened miscarriage and inadequate corpus luteum function during early pregnancy. Zaqout *et al*. [33] found that mothers of children born with congenital heart disease received more DYG during the first trimester of pregnancy than those in the control group. This raises concerns regarding the safety of DYG-based PPOS for the fetus.

In non-freeze-all cycles, fresh embryo transfer may be the preferred option for GnRH-ants when conditions allow, whereas the PPOS protocol uses a freeze-all strategy. It has also been confirmed that progestins are more cost-effective per live birth than antagonist cycles in planned freeze-all cycles [32].

Further research is needed to provide a more comprehensive evaluation of the PPOS protocol's efficacy, including the long-term outcomes and cost-effectiveness.

## 5. Conclusions

In conclusion, our study provides robust evidence that the PPOS protocol with DYG significantly improves oocyte maturation and retrieval outcomes while preserving the fertilization rate and embryo development efficiency comparable to the traditional GnRH-ant method. These findings suggested that the DYG-based PPOS protocol is an efficient alternative to the GnRH-ant protocol for controlled ovarian stimulation.

## Availability of Data and Materials

The data sets generated and analyzed during the current study are not publicly available as they are part of ongoing research, but are available from the corresponding author on reasonable request.

## Author Contributions

All authors contributed to the conception and design of the study. Material preparation and data collection were performed by TTT. The data analysis was performed by TNCD and TTT. The manuscript was written by TTT, DTL, HNTTN, TTKL, MHN and HL. 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

The study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Institutional Ethical Review Board of Hanoi Medical University (decision number: 842; reference IRB-VN01.001/IRB00003121/FWA 00004148). All participants were informed of the study details and provided informed consent before participation.


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## Conflict of Interest

The authors declare no conflict of interest.

## Declaration of AI and AI-assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGpt 3.5 (OpenAI, 2024) for grammar and spelling check. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/CEOG27951.

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