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ORIGINAL RESEARCH

Cumulative Live Birth Rates in Women Undergoing Progestin-Primed Ovarian Stimulation Using Medroxyprogesterone Acetate, Dydrogesterone, and Progesterone: A Retrospective Analysis

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Purpose: To investigate possible differences in cumulative live birth rates (CLBRs) among three progestins medroxyprogesterone acetate (MPA), dydrogesterone (DYG), and Progesterone within the progestin-primed ovarian stimulation (PPOS) protocol.

Patients and Methods: This retrospective study included 21,159 women undergoing one of three ovarian stimulation protocols, hMG + MPA, hMG + DYG, or hMG + Progesterone, between September 2013 and January 2024 in our centre. Patients received oral progestins once daily as per their assigned protocol with human menopausal gonadotropin initiated on menstrual cycle day 3. The primary outcome was the CLBR. Secondary outcomes comprised ovarian stimulation parameters, pregnancy outcomes per embryo transfer, and cumulative outcomes per individual.

Results: The CLBR demonstrated no statistically significant differences across the three progestin regimens: MPA (6409/14,930, 42.9%), DYG (1430/3205, 44.6%), and Progesterone (1297/3024, 42.9%; $p = 0.203$). Kaplan-Meier analysis revealed progressive CLBR accumulation through 5 frozen-thawed embryo transfer (FET) cycles, reaching 87.6%, 95.6%, and 93.7% for MPA, DYG, and Progesterone groups, respectively, with all groups achieving 50% CLBR by the second cycle. Cox regression adjusted for confounders confirmed comparable CLBR trajectories ($p > 0.05$), while multivariable logistic regression showed no association between progestin type and per-cycle live birth rate ($p > 0.05$). Notably, the Progesterone group exhibited elevated serum progesterone levels (trigger day: $p < 0.05$), whereas both DYG and Progesterone groups demonstrated higher LH levels than MPA ($p < 0.05$).

Conclusion: Our findings establish clinical equivalence in cumulative live birth outcomes among MPA, DYG, and Progesterone when implemented within the PPOS framework. This evidence supports protocol flexibility in progestin selection, enabling personalized decisions based on pharmacological characteristics, cost considerations, and patient tolerance.

Keywords: cumulative live birth rate, medroxyprogesterone acetate, dydrogesterone, progestin-primed ovarian stimulation, progesterons, frozen embryo transfer

Introduction

The prevention of premature luteinizing hormone (LH) surges and immature ovulation is fundamental to optimizing clinical outcomes for women undergoing in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). Building upon the physiological suppression of endogenous gonadotropins (Gn) by progesterone (P4) during the luteal phase,

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Kuang et al introduced the progestin-primed ovarian stimulation (PPOS) protocol, which combines hMG with exogenous progestins for ovarian stimulation (OS).[1] They found that the embryos originating from the PPOS protocol had similar developmental potential and could lead to comparable pregnancy outcomes as the short protocol.[1] Over time, multiple progestins have been validated for their efficacy. For instance, medroxyprogesterone acetate (MPA) effectively suppressed premature LH surges in 150 females undergoing controlled OS.[1] Furthermore, a randomized controlled trial (RCT) involving 516 first IVF/ICSI cycles established dydrogesterone (DYG) as a viable alternative progestin within the PPOS protocol.[2] Moreover, Progesterone soft capsules (marketed as Utrogestan) have effectively prevented premature LH surges in normal ovulatory females, offering a user-friendly regimen when combined with frozen-thawed embryo transfer (FET).[3,4]

Elevated P4 levels in the bloodstream after hCG administration are well-documented to adversely affect endometrial receptivity, thereby reducing the chances of successful pregnancy.[5] Exposure of the endometrium to P4 before oocyte retrieval during OS leads to premature decidualization, resulting in the closure of the implantation window well before a blastocyst can mature and reach the endometrial lining.[6] As elevated P4 on the trigger day is a hallmark of PPOS cycles, the protocol is routinely followed by FETs to overcome impaired endometrial receptivity. Improved cryopreservation techniques have expanded FET use in IVF, improving live birth rates.[7] Thus, the PPOS protocol combined with the "freeze-all" strategy has become effective in clinical settings.

The cumulative live birth rate (CLBR) represents the proportion of deliveries leading to at least one live birth per oocyte aspiration. It comprises all fresh and/or FETs until either a live birth is achieved or all embryos have been used, whichever occurs first.[5] Unlike analyses based on a single embryo transfer following oocyte retrieval, CLBR incorporates a broader range of outcomes, making it a more comprehensive measure for evaluating the effectiveness of the PPOS protocol. Moreover, CLBR is considered the most significant patient-centered outcome for evaluating the success of assisted reproductive technology cycles, offering patients more detailed and clinically relevant information regarding treatment success.[6]

The PPOS protocol has proven to offer several advantages since its development. Firstly, its oral administration significantly enhances patient convenience. Secondly, it markedly reduces the rate of ovarian hyperstimulation syndrome (OHSS), a chronic complication commonly related to traditional COH protocols.[8] A key factor in the success of the PPOS protocol lies in selecting the appropriate progestin. Although all progestins have the progestogenic effect in common, there are large pharmacological differences between progestins. Progesterone, which is produced and secreted naturally, can be detected in serum after oral or vaginal administration. Orally administered Progesterone, even in micronized form, shows a wide variation of absorption and bioavailability in the individual person.[9] In contrast, MPA and DYG are synthetic progestins that do not interfere with measurement of serum P4 value.[10] After oral administration, synthetic progestins are rapidly absorbed and attain a maximum serum concentration within 2–5 hours. In addition, they have a longer half-life than Progesterone and display stable plasma levels.[9]

Due to different chemical structures, MPA, DYG, and Progesterone have different binding affinities to steroid receptors and exert distinct biological effects.[11] Previous studies have revealed the efficiency of oral progestins (MPA, DYG, and Progesterone) in achieving comparable clinical pregnancy outcomes.[1,2,12,13] However, the limited sample sizes and incomplete FET cycles in previous studies have constrained their statistical value. Considering the distinct biological effects of various progestins, it is imperative to evaluate possible variances in CLBRs, which remain unexplored. Therefore, this large-scale study, involving 21,159 patients, examines the CLBRs associated with three widely used progestins—MPA, DYG, and Progesterone—within the PPOS protocol. We hypothesized that MPA, DYG, and Progesterone can yield comparable outcomes in the PPOS protocol combined with the "freeze-all" strategy. Our findings offer strong clinical evidence to guide practice and inform patient decisions on PPOS-based treatments.

Materials and Methods

Study and Patients

This study included 21,159 women who underwent one of three OS protocols, hMG + MPA, hMG + DYG, or hMG + Progesterone, between September 2013 and January 2024. It also set some exclusion criteria: the existence of moderate

or chronic endometriosis, abnormalities in the uterine cavity, cycles involving the use of different progestins, utilization of donor eggs or sperm, oocyte cryopreservation cycles, fresh embryo transfer, abnormal parental karyotypes, embryo transfers from two distinct stimulated cycles, absence of critical data or cases lost to follow-up.

Ovarian Stimulation Protocol and Oocyte Retrieval

Progestins were administered to all patients to prevent premature ovulation. Human menopausal gonadotropin (hMG; 150 to 225 IU/day; Anhui Fengyuan Pharmaceutical Co., China) was initiated on menstrual cycle day 3 (MC3) and continued until the trigger day, with dosages determined as per the individual baseline features. Further, patients received oral progestins once daily as per their assigned protocol: MPA; 4 mg/day; Shanghai Xinyi Pharmaceutical Co., China) in the hMG + MPA group,[14] DYG; 20 mg/day; Abbott Biologicals B.V., Netherlands) in the hMG + DYG group,[2] or Progesterone (100 mg/day; Laboratories Besins International, France) in the hMG + Progesterone group.[15] The hMG dosage was adjusted every 4 to 5 days based on transvaginal ultrasound and serum hormone evaluations. If there were more than 20 follicles with a diameter > 10 mm, we decreased the dosage of hMG from 225 to 150 IU. And if the FSH level was lower than 10 mIU/mL, we would add 75 IU to the original dose.[16] When ≥ 3 dominant follicles were achieved (≥18 mm diameter), oocyte maturation was triggered via triptorelin (0.1 to 0.2 mg; Decapeptyl, Ferring Pharma, China), human chorionic gonadotropin (hCG; 1000 to 5000 IU; Lizhu Pharma, China), or a combination of both. Triptorelin was used for women at high risk of developing OHSS.[17] For other patients, hCG or dual trigger was used at the discretion of clinicians.[1,18] Transvaginal ultrasound-guided oocyte retrieval was conducted 34 to 36 h post-trigger, and all follicles (≥10 mm diameter) were aspirated.[2,14,19]

Fertilization was conducted via IVF or ICSI depending on semen parameters and previous clinical history. ICSI was offered for the following indications: severe oligozoospermia, asthenozoospermia or teratozoospermia, obstructive azoospermia, poor semen quality on the day of oocyte pick-up, a history of prior fertilization failure with conventional insemination or a history of rescue ICSI. Early rescue ICSI was performed 4h after insemination when the second polar body was not evident in the retrieved oocytes combined with other signs of fertilization failure. Embryos were evaluated on day 3 after fertilization as per the Cummins criteria, which assess factors such as the number and regularity of blastomeres and the extent of embryonic fragmentation.[20] All top-quality cleavage-stage embryos were cryopreserved for FET. In cases where patients had ≥ 6 top-quality embryos, surplus top-quality embryos were allowed to grow till the blastocyst stage. Cleavage-stage embryos not meeting the criteria for top quality were subjected to extended culture. Only blastocysts depicting good morphology, as classified by the Gardner and Schoolcraft grading system, were cryopreserved on day 5 or 6.[21]

Protocol for Endometrial Preparation and FET

Endometrial preparation for FET was designed to each patient's clinical profile following oocyte retrieval. For patients with normal menstrual cycles (MCs), a natural cycle protocol was used, with continuous monitoring of follicular formation until ovulation was triggered. In cases where patients had a history of irregular MCs, a mild OS protocol was implemented, using letrozole (2.5 or 5 mg) for 5 days from MC3. Hormone replacement therapy was administered to patients with a thin endometrium or those who experienced failure in natural or mild stimulation cycles. Further, P4 was introduced 2 to 3 days after ovulation. Under the guidance of abdominal ultrasound, day 3 embryos were transferred 5 days post-ovulation, while blastocysts were transferred 7 days post-ovulation. After confirmation of pregnancy, luteal support was maintained until the 10th week of gestation.

Outcome Variables

Data extracted from medical records (electronic form) were used to compare baseline characteristics among the three groups, including age, infertility duration, body mass index (BMI), basal antral follicle count (AFC), basal follicle-stimulating hormone (FSH) levels, and causes of infertility. The primary outcome was the CLBR, characterized by the proportion of women achieving live births relative to the total number who underwent OS. Moreover, delivery of ≥ 1 baby or multiple births from a single female were counted as a single event for analysis. Secondary outcomes comprised OS parameters, pregnancy outcomes per embryo transfer, and cumulative outcomes per individual. A premature LH

surge was defined as serum LH levels > 10 IU/L before the day of trigger. The implantation rate was estimated as the ratio of gestational sacs detected via transvaginal ultrasound to the total number of transferred embryos.[22] Clinical pregnancy was defined as the presence of at least one intrauterine gestational sac analyzed by ultrasound at 6 weeks of gestation, while at least one fetus determined ongoing pregnancy with detectable cardiac activity on ultrasound beyond 10 weeks of gestation. The rate of miscarriage was estimated as the cases of miscarriages divided by the female's proportion achieving clinical pregnancy.[23]

Statistical Analysis

Data was statistically analyzed via IBM SPSS Statistics (v 26.0.0, IBM Corp., USA) and R software (v 4.2.2, Vienna, Austria). Cases with absence of critical data (< 3% of the cohort) were excluded from analysis. No data imputation was performed to avoid introducing bias, as the missingness rate was minimal and unrelated to core outcomes. Continuous variables were illustrated as mean ± SD or median with interquartile range, and groups were compared via one-way ANOVA or the Kruskal–Wallis test, as appropriate. Categorical variables were reported as numbers with percentages and analyzed via Pearson's chi-square test. Post hoc comparisons were adjusted using the Bonferroni correction.

Multivariable logistic regression analyses evaluated the effect of independent variables on live birth rates per single embryo transfer, with outcomes reported as odds ratios (ORs) and corresponding 95% CIs. A Cox proportional hazards model was employed to examine the effect of independent variables on CLBR, with results depicted as hazard ratios (HRs) and 95% CIs. Further, CLBR curves were constructed based on the number of FET cycles via Kaplan–Meier analysis. Subgroup analyses were carried out on two independent covariates. Participants were stratified into two age categories (< 35 and ≥ 35 years). For basal AFC, participants were divided into three groups (AFC ≤ 5, AFC 6 to 15, and AFC >15). Pairwise comparisons of cumulative incidence curves between groups were carried out via the Log rank test to determine the substantial variances. All statistical tests were two-tailed, and a p-value <0.05 represented a significance threshold.

Results

Baseline Features of Patients

The study flowchart is illustrated in Figure 1. Approximately 21,159 patients who met the study criteria (inclusion and exclusion) were selected for this analysis. The patients were assigned to 3 groups for comparison: (1) hMG + MPA (n =14,930 patients), (2) hMG + DYG (n = 3205 patients), and (3) hMG + Progesterone (n=3024 patients). All baseline features of the patients are detailed in Table 1. Over 50% of the women had primary infertility, and this number was consistent in all groups. Moreover, tubal factors were the primary cause of infertility, followed by mixed and male factors, a pattern observed uniformly across the groups. Compared with MPA and DYG groups, the Progesterone group were younger (Progesterone 32 [29, 35] years vs MPA 32 [29, 36] years vs DYG 32 [29, 36] years) but had the least AFC in ultrasound images (Progesterone 7 [4, 11] vs MPA 10 [7, 14] vs DYG 10 [6, 15]). Patients in the MPA group had higher BMI than DYG and Progesterone groups (MPA 21.72 [19.92, 24.03] kg/m2 vs DYG 21.48 [19.83, 23.64] kg/m2 vs Progesterone 21.45 [19.63, 23.56] kg/m2). An increasing number of women in the MPA group underwent OPU for the first time (MPA 12,166/14,930 [81.5%] vs DYG 2383/3205 [74.4%] vs Progesterone 2380/3024 [78.7%]). However, a more significant number of women in the Progesterone group underwent an IVF cycle (MPA 7687/14,930 [51.5%] vs DYG 1958/3205 [61.1%] vs Progesterone 2126/3024 [70.3%]).

Characteristics of the Ovarian Stimulation Cycle

Table 2 illustrates OS features in all groups. For IVF/ICSI treatment, Progesterone group consumed the least hMG (Progesterone 1650 [1350, 1875] IU vs MPA 2025 [1800, 2250] IU vs DYG 1800 [1500, 2025] IU). Progesterone, a natural micronized P4 detectable in serum after oral administration, was associated with higher serum P4 levels on the trigger day in the Progesterone group (Progesterone 3.70 [2.70, 5.02] ng/L vs MPA 0.60 [0.40, 0.80] ng/L vs DYG 0.60 [0.40, 0.80] ng/L). However, compared with MPA group, the serum LH level on the trigger day was higher in DYG and Progesterone groups (MPA 1.81 [1.10, 2.85] IU/L vs DYG 2.25 [1.31, 3.40] IU/L vs Progesterone 2.18 [1.25, 3.50] IU/L) and the incidence of premature LH surge had the same

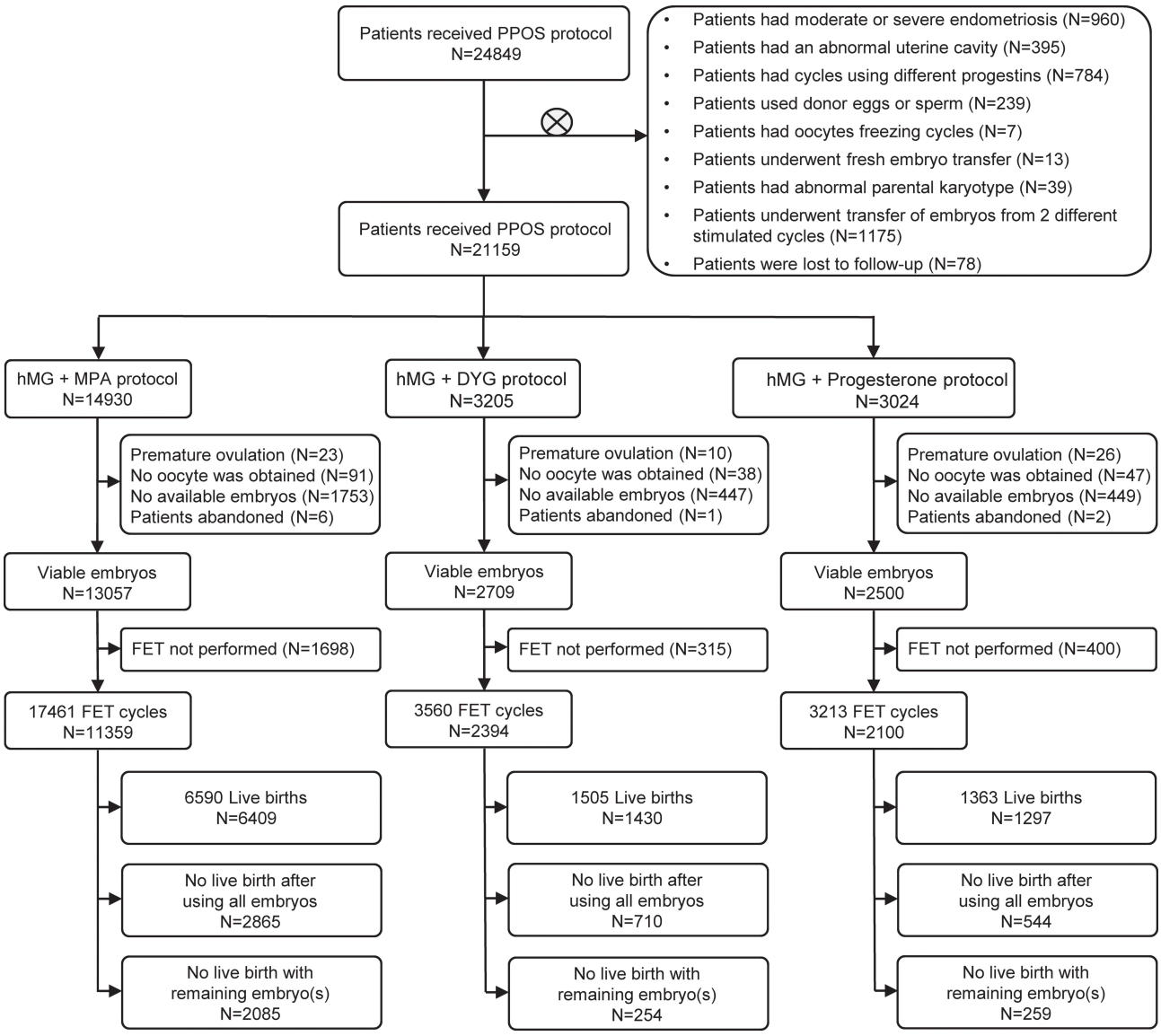

Figure 1 Flowchart of the study population with exclusion criteria and cumulative pregnancy outcomes. Patients using hMG + MPA, hMG + DYG or hMG + Progesterone for OS were included in the analysis, except those who did not meet the criteria. After one or more FET cycles, women were divided into 3 statuses.
Abbreviations: DYG, dydrogesterone; FET, frozen-thawed embryo transfer; MPA, medroxyprogesterone acetate; PPOS, progestin-primed ovarian stimulation.

trend (MPA 159/14,930 [1.1%] vs DYG 46/3205 [1.4%] vs Progesterone 83/3024 [2.7%]). Each group showed a distinct cancellation rate attributable to premature ovulation, failure to retrieve oocytes, lack of available embryos, or patient withdrawal. Moderate or severe OHSS incidence was not substantially different across the groups. Four patients in the MPA group, one in the DYG group, and three in the Progesterone group experienced moderate OHSS. One patient in the MPA group had severe OHSS during the treatment.

Women in the MPA group demonstrated higher values for serum estradiol levels on the trigger day, as well as more significant oocytes retrieved, fertilized, cleaving embryos, blastocysts formed, top-quality embryos, and available embryos compared to women in the DYG and Progesterone groups. Importantly, most patients in the MPA and DYG groups underwent OPU between 2016 and 2024. However, all patients in the Progesterone group underwent OPU between 2013 and 2019, a period significantly earlier, with no cases of Progesterone use during 2020–2024 included in the study.

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Table 1 Baseline Features of Women in the MPA, DYG, and Progesterone Groups

Demographic Characteristics	hMG + MPA	hMG + DYG	hMG + Progesterone	P value
Number of women, n	14930	3205	3024	——
Age of women (years)	32 (29, 36)[a]	32 (29, 36)[b]	32 (29, 35)[b]	< 0.001
< 35, n (%)	9975 (66.8)[a]	2205 (68.8)[ab]	2156 (71.3)[b]	
≥35, n (%)	4955 (33.2)[a]	1000 (31.2)[ab]	868 (28.7)[b]	
Infertility duration (years)	2 (1, 4)[a]	2 (1, 4)[b]	3 (1, 4)[a]	< 0.001
Primary infertility, n (%)	7880 (52.8)	1638 (51.1)	1609 (53.2)	0.174
Cycle number, n (%)				< 0.001
First cycle	12166 (81.5)[a]	2383 (74.4)[b]	2380 (78.7)[c]	
Repeated cycles	2764 (18.5)[a]	822 (25.6)[b]	644 (21.3)[c]	
Body mass index (kg/m^2)	21.72 (19.92, 24.03)[a]	21.48 (19.83, 23.64)[b]	21.45 (19.63, 23.56)[b]	< 0.001
Basal antral follicle count	10 (7, 14)[a]	10 (6, 15)[a]	7 (4, 11)[b]	< 0.001
Basal FSH level (IU/L)	5.64 (4.82, 6.60)[a]	5.64 (4.88, 6.64)[a]	5.49 (4.67, 6.48)[b]	< 0.001
Cause of infertility, n (%)				< 0.001
Tubal	6163 (41.3)[a]	1560 (48.7)[b]	1523 (50.4)[b]	
Ovulatory	1076 (7.2)[a]	125 (3.9)[b]	159 (5.3)[c]	
Endometrium factor	625 (4.2)[a]	125 (3.9)[a]	67 (2.2)[b]	
Male cause	2283 (15.3)[a]	448 (14.0)[a]	313 (10.4)[b]	
Mixed causes	2913 (19.5)[a]	702 (21.9)[b]	850 (28.1)[c]	
Unexplained	1870 (12.5)[a]	245 (7.6)[b]	112 (3.7)[c]	
Insemination method, n (%)				< 0.001
IVF	7687 (51.5)[a]	1958 (61.1)[b]	2126 (70.3)[c]	
ICSI	4943 (33.1)[a]	837 (26.1)[b]	710 (23.5)[c]	
IVF+ICSI	2300 (15.4)[a]	410 (12.8)[b]	188 (6.2)[c]	
Number of women having different FET cycles, n (%)				< 0.001
0	3569 (23.9)[a]	811 (25.3)[a]	924 (30.6)[b]	
1	6852 (45.9)[a]	1548 (48.3)[b]	1320 (43.7)[c]	
2	3241 (21.7)[a]	612 (19.1)[b]	534 (17.7)[b]	
3	0997 (6.7)[a]	165 (5.1)[b]	181 (6.0)[ab]	
4	0219 (1.5)[a]	54 (1.7)[a]	47 (1.6)[a]	
5	0052 (0.3)[a]	15 (0.5)[ab]	18 (0.6)[b]	

Notes: Data were depicted as mean (SD), median (first quartile, third quartile) or number (%). Continuous variables were tested by one-way ANOVA or the Kruskal–Wallis test. The chi-square test tested categorical variables. Post hoc analyses were performed using the Bonferroni test. Different letters a, b, and c represent significant group differences: $p < 0.05$.

Table 2 IVF/ICSI Cycle Features are Available in All Groups

Stimulation Characteristics	hMG + MPA (n=14930)	hMG + DYG (n=3205)	hMG + Progesterone (n=3024)	P value
Total hMG dosage (IU)	2025 (1800, 2250)[a]	1800 (1500, 2025)[b]	1650 (1350, 1875)[c]	< 0.001
Duration of stimulation (days)	11 (10, 12)[a]	11 (10, 11)[b]	11 (10, 12)[c]	< 0.001
Serum estradiol level on the trigger day (pg/mL)	2804 (1572, 4366)[a]	2531 (1469, 3858)[b]	2764 (1508, 4283)[a]	< 0.001
Serum progesterone level on the trigger day (ng/L)	0.60 (0.40, 0.80)[a]	0.60 (0.40, 0.80)[a]	3.70 (2.70, 5.02)[b]	< 0.001
Serum LH level on the trigger day (IU/L)	1.81 (1.10, 2.85)[a]	2.25 (1.31, 3.40)[b]	2.18 (1.25, 3.50)[b]	< 0.001
Incidence of premature LH surge, n (%)	00159 (1.1)[a]	46 (1.4)[a]	83 (2.7)[b]	< 0.001
Cancellation rate, n (%)	1873 (12.5)[a]	496 (15.5)[b]	524 (17.3)[c]	< 0.001
Incidence of premature ovulation	23 (1.2)[a]	10 (2.0)[a]	26 (5.0)[b]	
No oocyte was obtained	91 (4.8)[a]	38 (7.7)[b]	47 (9.0)[b]	
No available embryos	1753 (93.6)[a]	447 (90.1)[b]	449 (85.7)[c]	
Patients abandoned	6 (0.3)[a]	1 (0.2)[a]	2 (0.4)[a]	
Incidence of moderate or severe OHSS	05 (0.0)	1 (0.0)	3 (0.1)	0.222
Year of OPU, n (%)				< 0.001
2013–2015	940 (6.3)[a]	379 (11.8)[b]	831 (27.5)[c]	
2016–2019	8442 (56.5)[a]	2609 (81.4)[b]	2193 (72.5)[c]	
2020–2024	5548 (37.2)[a]	217 (6.8)[b]	0 (0.0)[c]	

(*Continued*)

Table 2 (Continued).

Stimulation Characteristics	hMG + MPA (n=14930)	hMG + DYG (n=3205)	hMG + Progesterone (n=3024)	P value
No. of oocytes obtained	9 (5, 15)[a]	8 (4, 13)[b]	8 (4, 13)[b]	< 0.001
No. of oocytes fertilized	7 (3, 11)[a]	6 (3, 10)[b]	6 (3, 10)[b]	< 0.001
Fertilization rate per group, % (n)	82.6 (117331/142123)[a]	80.5 (22635/28107)[b]	78.7 (21489/27299)[c]	< 0.001
No. of cleaving embryos	6 (3, 10)[a]	5 (3, 9)[b]	5 (2, 9)[b]	< 0.001
Cleavage rate per group, % (n)	89.9 (105506/117331)[a]	87.8 (19866/22635)[b]	89.8 (19290/21489)[a]	< 0.001
No. of blastocyst formation	0 (0, 2)[a]	0 (0, 1)[b]	0 (0, 1)[b]	< 0.001
Blastocyst formation per group, % (n)	28.6 (17619/61542)[a]	25.0 (2819/11273)[b]	25.0 (2705/10823)[b]	< 0.001
No. of top-quality embryos	2 (1, 5)[a]	2 (1, 4)[b]	2 (1, 4)[c]	< 0.001
No. of available embryos	3 (1, 6)[a]	3 (1, 5)[b]	3 (1, 5)[b]	< 0.001

Notes: Data were depicted as mean (SD), median (first quartile, third quartile) or number (%). Continuous variables were tested by one-way ANOVA or the Kruskal–Wallis test. Categorical variables were tested using the chi-square test. Post hoc analyses were carried out using the Bonferroni test. Different letters a, b, and c represent substantial variances between groups: $p < 0.05$.

Abbreviations: DYG, dydrogesterone; MPA, medroxyprogesterone acetate; OHSS, ovarian hyperstimulation syndrome; OPU, oocyte pick-up.

Pregnancy Outcomes

Approximately 24,234 FET cycles involving the transfer of 40,766 embryos were completed in all groups. The percentages of embryos transferred per cycle and the embryo stage at transfer varied significantly among the groups. The MPA group depicted a higher biochemical pregnancy rate per cycle, whereas the DYG group revealed higher clinical and ongoing pregnancy rates per cycle. The Progesterone group had higher multiple pregnancy and live birth rates per transfer. All three groups showed comparable implantation and ectopic pregnancy rates (Table 3).

Multivariable logistic regression analyses, incorporating variables such as stimulation protocol, patient age, infertility duration, infertility types, cycle number, BMI, AFC, basal FSH levels, cause of infertility, insemination method, serum estradiol, and P4 levels on the trigger day, year of OPU, number of oocytes retrieved, top-quality embryos, available embryos, embryos transferred, stage at transfer, endometrial preparation, and endometrial thickness, demonstrated that the type of progestin used in the PPOS protocol was not considerably related to live birth rate per FET cycle ($p > 0.05$) (Figure 2).

CLBRs of Different Groups

No substantial variations were observed in the CLBR among the three groups (MPA 6409/14,930 [42.9%] vs DYG 1430/3205 [44.6%] vs Progesterone 1297/3024 [42.9%], $p = 0.203$). However, the time from initiating stimulation to the first live birth was considerably shorter in the MPA group (Table 3). Cox model with the potential confounding factors, ie,

Table 3 Main Reproductive Outcomes After Frozen Embryo Transfer

Characteristics	hMG + MPA (n=14930)	hMG + DYG (n=3205)	hMG + Progesterone (n=3024)	P value
Total no. of embryos transferred	28689	6174	5901	——
Total no. of transfer cycles	17461	3560	3213	——
No. of embryos transferred per cycle, n (%)				< 0.001
Single	6233 (35.7)[a]	946 (26.6)[b]	525 (16.3)[c]	
Double	11228 (64.3)[a]	2614 (73.4)[b]	2688 (83.7)[c]	
Embryo stage at transfer, n (%)				< 0.001
Cleavage stage	13129 (75.2)[a]	2977 (83.6)[b]	2731 (85.0)[b]	
Blastocyst stage	4273 (24.5)[a]	578 (16.2)[b]	466 (14.5)[c]	
Combined	59 (0.3)[ab]	5 (0.1)[b]	16 (0.5)[a]	
Endometrial preparation, n (%)				< 0.001
Natural cycle	2212 (12.7)[a]	562 (15.8)[b]	1374 (42.8)[c]	
Mild stimulation cycle	8922 (51.1)[a]	1675 (47.1)[b]	1134 (35.3)[c]	
Hormone replacement cycle	6327 (36.2)[a]	1323 (37.2)[a]	705 (21.9)[b]	

(*Continued*)

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Table 3 (Continued).

Characteristics	hMG + MPA (n=14930)	hMG + DYG (n=3205)	hMG + Progesterone (n=3024)	P value
Endometrial thickness (mm)	10.3 (9.0, 12.0)[a]	10.1 (8.8, 11.7)[b]	11.0 (9.4, 12.8)[c]	< 0.001
(a) Pregnancy outcome per cycle, n (%)				
Biochemical pregnancy rate per cycle	1061 (6.1)[a]	138 (3.9)[b]	56 (1.7)[c]	< 0.001
Clinical pregnancy rate per cycle	8649 (49.5)[a]	1869 (52.5)[b]	1674 (52.1)[b]	< 0.001
Ongoing pregnancy rate per cycle	7560 (43.3)[a]	1646 (46.2)[b]	1472 (45.8)[b]	< 0.001
Implantation rate	10409/28,689 (36.3)	2321/6174 (37.6)	2142/5901 (36.3)	0.147
Miscarriage rate	1212 (14.0)[a]	228 (12.2)[b]	261 (15.6)[a]	0.014
Multiple pregnancy rate	1877 (21.7)[a]	424 (22.7)[a]	475 (28.4)[b]	< 0.001
Ectopic pregnancy rate	216 (2.5)	54 (2.9)	38 (2.3)	0.478
Live birth rate per cycle	6590 (37.7)[a]	1505 (42.3)[b]	1363 (42.4)[b]	< 0.001
(b) Cumulative outcome, n (%)				
Biochemical pregnancy rate per woman	1006 (6.7)[a]	132 (4.1)[b]	53 (1.8)[c]	< 0.001
Clinical pregnancy rate per woman	7837 (52.5)[a]	1688 (52.7)[a]	1498 (49.5)[b]	0.010
Ongoing pregnancy rate per woman	7192 (48.2)[a]	1549 (48.3)[a]	1367 (45.2)[b]	0.009
Cumulative live birth rate	6409 (42.9)	1430 (44.6)	1297 (42.9)	0.203
(c) Time to pregnancy from starting stimulation (months)				
Time to first clinical pregnancy	5.7 (4.4, 7.8)[a]	6.4 (4.8, 8.7)[a]	7.1 (5.6, 9.8)[b]	< 0.001
Time to first ongoing pregnancy	6.7 (5.3, 9.1)[a]	7.5 (5.8, 10.0)[a]	8.2 (6.6, 11.0)[b]	< 0.001
Time to first live birth	12.9 (11.4, 15.4)[a]	13.6 (11.9, 16.3)[ab]	14.4 (12.6, 17.3)[b]	< 0.001
No. of FET cycle(s) to first live birth	1 (1, 2)[a]	1 (1, 2)[b]	1 (1, 2)[b]	< 0.001

Notes: Data were depicted as mean (SD), median (first quartile, third quartile) or number (%). Continuous variables were tested by one-way ANOVA or the Kruskal–Wallis test. Categorical variables were tested using the chi-square test. Post hoc analyses were performed using the Bonferroni test. Different letters a, b, and c represent substantial variances between groups: $p < 0.05$.
Abbreviations: DYG, dydrogesterone; FET, frozen embryo transfer; MPA, medroxyprogesterone acetate.

stimulation protocol, age, infertility duration, type of infertility, cycle number, BMI, AFC, infertility causes, basal FSH, insemination method, serum estradiol, and P4 level on the trigger day, year of OPU, number of oocytes obtained, top-quality embryos, number of available embryos and FET cycles revealed that the use of MPA, DYG or Progesterone in PPOS protocol could lead to comparable CLBRs ($p > 0.05$). When the MPA group served as the reference group, the DYG and Progesterone groups showed lower CLBRs, but they did not reach a substantial variation (DYG aHR=0.977; 95% CI [0.921, 1.037]; Progesterone aHR = 0.993; 95% CI [0.915, 1.077]) (Figure 3).

As per the Kaplan-Meier analysis, the CLBRs after 5 FET cycles were 87.6%, 95.6%, and 93.7% for the MPA, DYG, and Progesterone groups. Pairwise comparisons between the MPA and DYG groups, as well as between the MPA and Progesterone groups, yielded statistically significant results (p [MPA/DYG] < 0.05; p [MPA/Progesterone] < 0.01). The second cycle reached the time required to obtain a 50% CLBR for all three groups (Figure 4A).

Subgroup Analysis

In the Kaplan-Meier analysis stratified by age, it was observed that the CLBRs over five cycles were comparable among the groups for women aged < 35 years (MPA 90.1%; DYG 96.4%; Progesterone 93.4%, p = 0.28). The time required to obtain a 50% CLBR for all groups was reached by the second cycle (Figure 4B). In women aged ≥ 35 years, the CLBRs over five cycles were 78.5%, 89.5%, and 85.1% for the MPA, DYG, and Progesterone groups, respectively. A pairwise comparison between the MPA and DYG groups showed substantial variations (p < 0.01). The DYG group reached a 50% CLBR by the second cycle, whereas the MPA and Progesterone groups achieved this by the third cycle (Figure 4C).

After stratifying by AFC, for women with AFC ≤ 5, the CLBRs over five cycles were 69.8%, 93.6%, and 83.5% in MPA, DYG, and Progesterone groups, respectively. The pairwise comparison between MPA and DYG group and the comparison between MPA and Progesterone group showed substantial variances (p [MPA/DYG] < 0.01; p [MPA/Progesterone] < 0.01) (Figure 4D). For women with AFC 6–15, the CLBRs over five cycles were 87.3%, 94.1% and 94.5% respectively in MPA, DYG and Progesterone group. The comparison between MPA and Progesterone group and

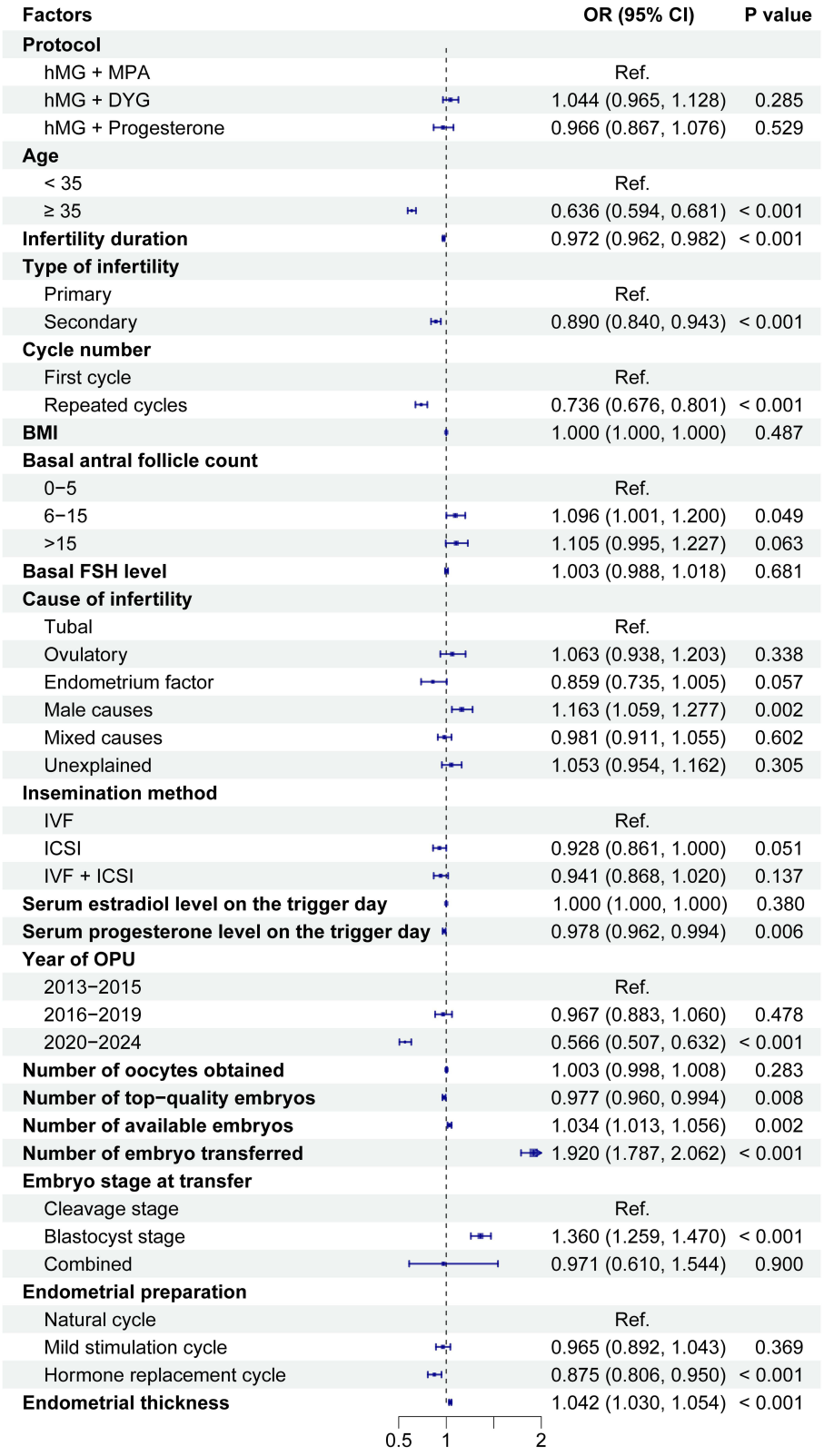

Figure 2 Forest plot of live birth rate per FET cycle using multivariable logistic regression analyses.
Abbreviations: DYG, dydrogesterone; MPA, medroxyprogesterone acetate; OPU, oocyte pick-up; OR, odds ratio; Ref., reference.

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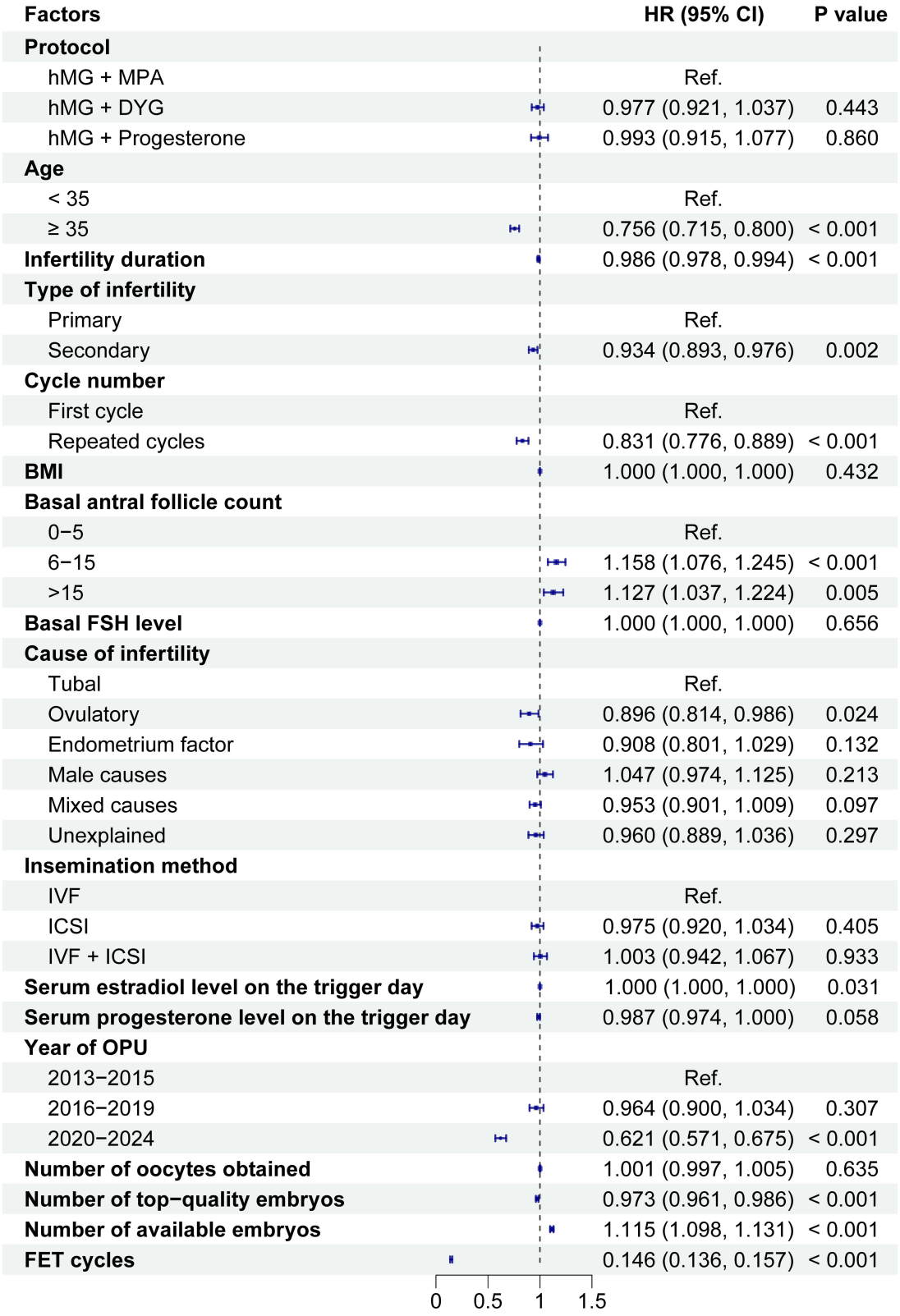

Figure 3 Forest plot of cumulative live birth rate per woman using the Cox proportional hazard model.
Abbreviations: DYG, dydrogesterone; HR, hazard ratio; MPA, medroxyprogesterone acetate; OPU, oocyte pick-up; Ref., reference.

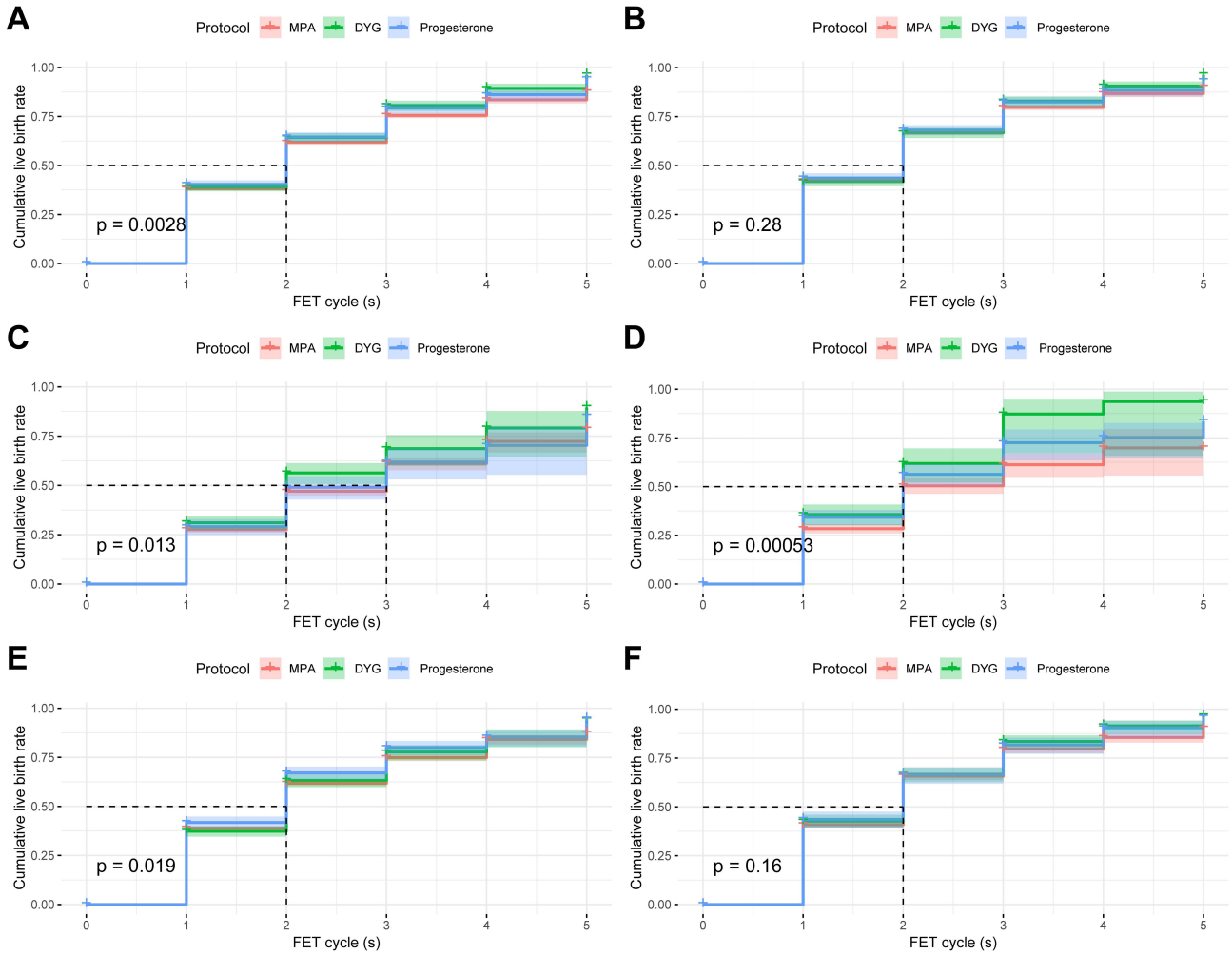

Figure 4 CLBR over five FET cycles for patients using PPOS protocol with different progestins. (**A**) CLBRs of all the patients; (**B**) CLBRs in women aged <35 years; (**C**) CLBRs in women aged ≥35 years; (**D**) CLBRs in women with AFC ≤5; (**E**) CLBRs in women with AFC 6–15; (**F**) CLBRs in women with AFC >15.
Abbreviations: AFC, antral follicle count; DYG, dydrogesterone; MPA, medroxyprogesterone acetate; PPOS, progestin-primed ovarian stimulation.

the comparison between DYG and Progesterone group yielded significant results (p [MPA/Progesterone] < 0.01; p [DYG/Progesterone] < 0.05) (Figure 4E). For women with AFC > 15, the CLBRs after more than five cycles were 90.3%, 96.6%, and 95.9% for the MPA, DYG, and Progesterone groups, respectively, with no substantial variances between the groups (p > 0.05) (Figure 4F). Across all 3 AFC strata, the time required to obtain a 50% CLBR was consistently the second cycle for all 3 groups (Figure 4D–F).

Discussion

As the pioneer of the PPOS protocol, our center has established the most extensive medical database of patients treated with various progestins.[24] The present study represents the first comprehensive comparison of CLBRs among women undergoing OS with 3 distinct progestins: MPA, DYG, and Progesterone. By establishing CLBR per woman as the primary outcome, this study provided a comprehensive and clinically significant reference for implementing the PPOS protocol in reproductive medicine. This retrospective study demonstrated that different progestins, MPA, DYG, and Progesterone, used within the PPOS protocol achieve comparable CLBR when combined with embryo cryopreservation in females undergoing COH.

The PPOS protocol, introduced in 2015, used MPA with hMG to efficiently prevent premature LH surges during OS.[1] MPA is marked by its moderate to strong progestogenic activity, minimal androgenic properties, and non-interference with the evaluation of endogenous P4 production.[10] After that, DYG and Progesterone were validated as viable oral

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alternatives for PPOS.[2–4,12,15] DYG, a synthetic progestin structurally analogous to endogenous P4, is observed for its stable plasma concentrations and lack of interference with serum P4 measurements. Moreover, it is safe and free of androgenic effects, even at elevated dosages. Progesterone, a natural micronized progestin, shows dose-independent detection in serum after either oral or vaginal administration.[12] Thus, this study demonstrated that the Progesterone group had considerably higher serum P4 levels on the trigger day. Furthermore, patients in the Progesterone group were advised to take the medication once daily at bedtime to reduce the risk of dizziness and sleepiness and to perform blood tests in the morning rather than at a specific time. The uncertain interval between the last dose and blood collection may affect the serum P4 levels, thereby affecting the accuracy of the test results.[15]

This study revealed that the serum LH levels on the trigger day were remarkably reduced in the MPA group compared to the other two groups. Consistent with this, an RCT involving 516 first IVF/ICSI cycles reported that, at each observation point during OS, the average LH levels in the DYG group were substantially higher than in the MPA group.[2] Guo et al observed 1188 cycles and found that the LH levels on the trigger day in the Progesterone group were considerably higher than in all MPA group subgroups, except patients under 35 years. However, no substantial variations were found in basal LH levels between the groups.[13] Moreover, when comparing the use of DYG and Progesterone in the PPOS protocol, Zhu et al found that both groups had similar average LH levels on the trigger day and the day after stimulation.[12] Another RCT involving 450 females with advanced endometriosis reported that LH levels on the trigger day were lower in the MPA group than in the DYG and Progesterone groups, with the Progesterone group showing higher LH levels.[25]

The findings suggest that DYG and Progesterone may result in less pronounced pituitary suppression than MPA during OS. This phenomenon could be attributed to variations in GnRH secretion patterns modulated by different progestins. The biological role of P4 at the cellular level is initiated by intracellular P4 receptors (PRs), and the binding affinity of progestins to PRs differs among compounds, thereby influencing their biological activity.[2,9] Relative to promegestone (set at 100%), the binding affinities of Progesterone, DYG, and MPA to PRs in circulation are approximately 50, 75, and 115%, respectively.[9] It is hypothesized that in the hypothalamus, the binding affinities of DYG and Progesterone are similarly lower than that of MPA. However, further research is needed to validate this hypothesis. Furthermore, in the Progesterone group, an elevated LH level on the trigger day may partially be explained by Progesterone's interference with serum P4 measurement, potentially leading to an underestimation of premature luteinization. Consistent with this, the present results revealed considerably higher incidences of premature LH surge and ovulation in the Progesterone group (Table 2).

In this study, multivariable logistic regression analyses and the Cox proportional hazards model evaluated the effects of different progestins on pregnancy outcomes. After adjusting for confounding variables, using various progestins in the PPOS protocol did not result in substantial variations in live birth rate per cycle or CLBR. Importantly, a negative correlation was observed between serum P4 levels on the trigger day and the live birth rate per cycle. Premature P4 elevation (PE) during the late follicular phase is relatively common, and emerging evidence indicates that PE on the trigger day may adversely impact pregnancy outcomes in fresh IVF/ICSI cycles.[5] This effect is hypothesized to stem primarily from the impact of elevated peripheral P4 levels on the endometrium and the window of implantation, potentially causing asynchrony between the endometrium and developing embryos.[26] However, in FET cycles, a study examining women undergoing OS with GnRH analogues and Gn found no evidence of a negative association between premature PE on the trigger day during the IVF/ICSI cycle and the possibility of achieving pregnancy after the transfer of frozen-thawed embryos derived from that cycle.[5] Lu et al conducted a retrospective analysis of 4106 treatment cycles involving hMG and MPA, followed by FET. They found that elevated P4 levels on the trigger day did not adversely affect pregnancy cycles.[27] Another study closely aligned with the current findings, analyzed 504 PGT cycles, and demonstrated that the high-P4 group showed substantially lower live birth and clinical pregnancy rates than the low-P4 group in the first FET cycle.[28] This negative correlation between premature PE and pregnancy outcomes in FET cycles suggests that PE may negatively affect embryo quality. However, the precise impact of PE on embryo quality remains a subject of ongoing debate.

The freeze-all strategy is considered an optimal solution to rescue the role of late follicular elevated P4 on endometrial receptivity. The current analysis aligns with previous studies, demonstrating that premature PE on the

trigger day during the OS cycle does not compromise the CLBR when a "freeze-all" strategy is employed.[29–31] The mechanism underlying the rise in serum P4 remains a topic of debate; however, one possible explanation is the increase in follicle numbers resulting from controlled COH.[27] It is predicted that the impact of premature PE on embryo quantity may offset its detrimental effects on embryo quality. Thus, in this study, serum P4 levels on the trigger day were unrelated to the CLBR but negatively correlated with the live birth rate per cycle. Excluding the Progesterone group, as Progesterone may interfere with P4 measurements, the study observed that 18.54% of women in the hMG + MPA group and 17.44% in the hMG + DYG group revealed elevated P4 levels (≥ 1 ng/mL). These findings are aligned with a previous study, which depicted a similar incidence of elevated P4 levels (17.78%) in hMG + MPA treatment cycles.[27] It was indicated that PE was a frequent phenomenon in the PPOS protocol, and further studies are required to examine the impact of this phenomenon on the application of exogenous progestins.

However, women receiving MPA demonstrated a shorter time to obtain a live birth. The considerable impact of individual factors prompted us to perform a Kaplan-Meier analysis and plot CLBR curves based on the number of FET cycles. A distinct upward trend in CLBRs was observed across all three groups, with an increase in FET cycles. CLBRs rose substantially during the first two FET cycles, followed by a more gradual increase over the next 3–5 cycles. By the second FET cycle, all groups achieved a success rate of at least 50%. Furthermore, a subgroup analysis evaluated CLBRs in women of varying ages and ovarian reserve. The most pronounced differences were observed in women aged ≥ 35 years and those with an AFC of ≤5, where the administration of DYG was associated with improved cumulative pregnancy outcomes. However, further evidence is required to substantiate this finding. Moreover, a positive correlation between CLBR and younger age and higher AFC was evident across all three groups. AFC, an ultrasound-based marker of follicle number, is extensively used as a reliable indicator of ovarian reserve. A reduced AFC is typically related to a low response to OS during IVF/ICSI. Chang et al reported a trend toward lower pregnancy rates in females with fewer antral follicles.[32,33] Similarly, this study revealed a downward trend in CLBRs among women with a low AFC. Further, the AFC ≤ 5 group had a higher proportion of women of advanced age, which may also contribute to the lower CLBR observed in this group (AFC ≤ 5 group: 35 [32, 40] years vs AFC 6 to 15: 32 [29, 35] years vs AFC >15: 30 [28, 33] years). The current results reinforce the capacity of AFC as a predictive tool for pregnancy outcomes in IVF/ICSI.

In term of the safety of OS, MPA, DYG, and Progesterone showed comparable results of OHSS incidence. So far, the PPOS protocol had been proven to have the advantage of reducing the incidence of OHSS. A previous RCT conducted by Wang et al reported no patients suffered from moderate of severe OHSS in the PPOS group, but 2 patients using short agonist protocol developed moderate OHSS.[10] Another RCT comparing PPOS to the antagonist protocol in PCOS patients, who are at high risk of experiencing OHSS, obtained similar outcomes that mild and moderate OHSS were less in the PPOS group.[34] However, the mechanisms by which progesterone prevents OHSS is still unknown and further investigations is needed.

This study was limited by its single-center, retrospective design, subject to inherent biases and potential unmeasured confounders. However, baseline features showed substantial variations, which may be attributed to the disproportionately larger sample size enrolled in the MPA group than the other groups, amplifying these differences. The Kaplan-Meier analysis, which indicated that patients who did not resume treatment had a similar possibility of achieving a live birth as those who continued, may overestimate the CLBR.[24] Progesterone has seen a decline in use for OS due to its side effects, such as dizziness, and its interference with serum P4 measurement. An imbalance in the distribution of OPU years was also observed in our dataset. Seasonal factors like the climate, temperature and food may further affect patients, leading to seasonal variations in pregnancy outcomes. The proportion of women who did not achieve a live birth despite having remaining embryos was higher in the MPA group (MPA 14.0% vs DYG 7.9% vs Progesterone 8.6%). Allowing for a longer follow-up period may result in a more comparable CLBR across the groups. Besides these limitations, the results of this study have substantial clinical applications, as the PPOS protocol is widely used worldwide. To the best of the current information, this was the first study to compare CLBRs in the PPOS protocol using three different progestins.

Conclusion

In conclusion, this study demonstrates that using three distinct progestins, MPA, DYG, and Progesterone, within the PPOS protocol combined with a "freeze-all" strategy yields comparable CLBRs in women undergoing IVF. These findings highlight the potential interchangeability of MPA, DYG, and Progesterone as viable options in OS protocols, offering flexibility in clinical settings while maintaining efficacy in achieving successful pregnancy outcomes. Our results

suggest that premature PE is relatively common in the PPOS protocol. It is negatively correlated with the live birth rate per cycle while unrelated to the CLBR. Further studies are needed to explore the potential mechanisms behind the rise and its impact on embryo quality and long-term outcomes.

Data Sharing Statement

All data sharing upon reasonable request should be directed to the corresponding author via Email at lemon_1114@126.com.

Ethics Statement

This extensive retrospective study used the Department of Assisted Reproduction clinical database at the Ninth People's Hospital, affiliated with Shanghai Jiao Tong University School of Medicine. The database was fully anonymized, ensuring no personally identifiable data was available to the investigators. In accordance with the Declaration of Helsinki, the study procedure was approved by the Institutional Review Board and the Ethics Committee of the respective hospital. Written informed consent was obtained from patients before using their data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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