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Euploidy rate and pregnancy outcomes in preimplantation genetic testing for aneuploidy cycles using progestin-primed ovarian stimulation versus GnRH antagonist protocol

Hu Tan[1], Li Huang[1], Wenjuan Liu[1], Jin Yan[1], Li Li[1], Yujiang Wang[1], Yuqiang Huang[1], Zonghui Xiao[1], Fenghua Liu[1*] and Xiqian Zhang[1*]

Abstract

Background Previous studies has yielded contradictory findings regarding the relationship between controlled ovarian hyperstimulation (COH) protocol and euploid blastocyst rate. This study aimed to investigate whether progestin-primed ovarian stimulation (PPOS) influences the euploidy rate and pregnancy outcomes in preimplantation genetic testing for aneuploidy (PGT-A) cycles compared to GnRH antagonist protocol.

Methods The retrospective study analyzed data from 598 PGT-A cycles conducted between January 2017 and October 2022 utilizing either PPOS (medroxyprogesterone acetate) or the GnRH antagonist protocol. The biopsied trophectoderm from 2218 blastocysts was collected for euploidy analysis via next-generation sequencing.

Results Biopsied blastocyst number was comparable between PPOS group and GnRH antagonist group (3.51 ± 2.93 vs. 3.91 ± 3.19, $P = 0.116$), although PPOS yielded fewer MII oocytes (10.27 ± 6.59 vs. 11.60 ± 6.71, $P = 0.015$). The euploidy rate (43.3% vs. 45.0%, $P = 0.423$), aneuploidy rate (36.9% vs. 36.0%, $P = 0.127$), and mosaic rate (19.4% vs. 17.6%, $P = 0.127$) were similar between the PPOS and GnRH antagonist protocols. Additionally, PPOS demonstrated comparable pregnancy outcomes to GnRH antagonist protocol, including clinical pregnancy rates (58.1% vs. 59.8%, $P = 0.713$) and live birth rates (51.1% vs. 46.9%, $P = 0.364$). But lower miscarriage rate was shown in the PPOS protocol (7.9% vs. 16.8%, $P = 0.019$).

Conclusions The PPOS protocol did not negatively impact euploid blastocyst formation or pregnancy outcomes compared to the GnRH antagonist protocol, indicating that medroxyprogesterone acetate was an alternate option to antagonists for women undergoing PGT-A.

*Correspondence:
Fenghua Liu
liushine2006@163.com
Xiqian Zhang
zhangxiqian2015@163.com

Full list of author information is available at the end of the article

Key messages

1.The blastocyst formation and genetic status were similar between the PPOS and GnRH antagonist protocols, including biopsied blastocyst number, euploidy rate, aneuploidy rate, and mosaic rate.

2.PPOS demonstrated comparable pregnancy outcomes to GnRH antagonist protocol, including clinical pregnancy rates and live birth rates.

3.A lower miscarriage rate was observed in the PPOS protocol compared to the GnRH antagonist protocol, indicating a potential advantage of PPOS protocol.

Keywords Progestin primed ovarian stimulation, GnRH antagonist, Preimplantation genetic testing for aneuploidy, Euploidy rate, Pregnancy outcome

Introduction

Controlled ovarian hyperstimulation (COH) is crucial in assisted reproductive technology (ART) for collecting multiple oocytes and producing sufficient transferable embryos. In conventional protocols, gonadotrophin-releasing hormone (GnRH) analogs, including GnRH agonists and antagonists, are administered to prevent ovulation by suppressing the pituitary LH surge. However, daily subcutaneous injection during COH can impose a significant physical and psychological burden on infertile women and incur a high cost [1]. Additionally, many patients are concerned about incorrect administration and its side effects [2].

Progestin-primed ovarian stimulation (PPOS) was introduced as a new COH protocol by Kuang et al. in 2015 [3], utilizing progestin to suppress the LH surge instead of GnRH analogs. A recent review reported that the clinical effectiveness and safety of PPOS were comparable to conventional protocols in several aspects, including the prevention of early luteinization, response to ovarian stimulation, and reproductive outcomes [4]. Medroxyprogesterone acetate (MPA), micronized progesterone, or dydrogesterone are administered orally, which lowers patient costs and discomfort compared to subcutaneous injection of GnRH agonist or antagonist. However, a notable drawback is the absence of fresh embryo transfer due to the known detrimental effect of progesterone on the endometrium [5].

With the need for frozen embryos during genetic testing, PPOS seems to be a patient-friendly and cost-effective option for those undergoing preimplantation testing for aneuploidy (PGT-A) [6]. However, recent studies have reported inconsistent results on the genetic status of embryos and pregnancy outcomes and PPOS [7–9]. For instance, Pai et al. reported a lower euploidy rate in the PPOS group among patients over 38 years old [7]. Yang et al. reported similar euploidy rates across different age groups between the PPOS and GnRH antagonist group [9]. In a study published by Giles et al. [8], the euploidy rate in the PPOS group was comparable to that in the GnRH antagonist group but the aneuploidy rate was lower in the PPOS group. A recent study revealed a higher euploidy rate and a lower mosaic rate in the PPOS group compared to the GnRH antagonist group [10].

To enhance the available evidence regarding the suitability of PPOS as a treatment for patients undergoing PGT-A, we conducted this study to investigate the genetic status of embryos and pregnancy outcomes in PPOS.

Materials and methods

Study participants

This retrospective cohort study was conducted at the Reproductive Medical Center of Guangdong Women and Children Hospital between January 2017 and October 2022. Women undergoing PGT-A were enrolled when at least one of the following criteria was met: 1) advanced maternal age (≥ 38 years old);2)recurrent miscarriage (≥ 2 or 3 consecutive miscarriages); 3) repeated implantation failure (≥ 4 embryos transferred or ≥ 3 blastocysts transferred without success). The exclusion criteria included: (1) maternal or paternal monogenic disease or chromosomal abnormalities; (2) cancellation of blastocyst culture due to no fertilized embryos or other reasons; (3) recipient of oocyte donation. This study was approved by the institutional review board of the Guangdong Women and Children Hospital (No. 202401380) and was conducted in compliance with the principles of the Declaration and Helsinki.

Protocol

The women began PGT-A with ovarian stimulation using either the PPOS or antagonist protocol. For the PPOS protocol, MPA (10 mg/day, Sphsineharm, Shanghai, China) was administered from the start of ovarian stimulation until the day of ovulation trigger. For the GnRH antagonist protocol, Ganirelix (0.25 mg/day, N.V.Organon, Oss, the Netherlands) or Cetrorelix (0.25 mg/day, Merck, Amsterdam, the Netherlands) was administrated from the fifth or sixth day of ovarian stimulation until the day of ovulation trigger. Ovarian stimulation commenced on the second or third day of the menstrual cycle. The initial dose of recombinant follicle stimulating hormone (FSH) (Puregon, Organon, Dubin, Ireland or Gonal F, Merck Serono S.P.A, Modugno, Italy)

or human menopausal gonadotropin (HMG, Lizhu Pharmaceutical Trading Co., Zhuhai, China) was determined based on the patient's age, body mass index (BMI) and ovarian reserve test values. Human chorionic gonadotropin (HCG 4000–10000 IU, Lizhu Pharmaceutical Trading Co., Zhuhai, China) and/or triptorelin (0.2 mg, Decapetyl, Ferring Pharmaceuticals, the Netherlands) were administered when at least two follicles reached ≥ 18 mm in diameter. Oocyte retrieval was performed approximately 36 h later.

Semen samples were prepared via either the swim-up method or the density gradient centrifugation method, following the kit instructions. Intracytoplasmic sperm injection (ICSI) was performed on metaphase II oocytes after 2–4 h of oocyte retrieval. Fertilization was confirmed by the presence of two pronuclei 16–18 h post insemination. Embryo culture continued until the blastocyst stage and trophectoderm biopsy was carried out on day 5 or 6. Blastocysts were graded according to the Gardner standard [11], and samples were analyzed using next-generation sequencing. Blastocysts were vitrified until results were available. More than 4 Mb chromosomal segments were detected and reported. Mosaic embryos were considered when the abnormal rate in the biopsied sample was 30% ~ 70%. The detailed procedures can be found in the previous study [12].

Frozen embryo transfer and outcomes follow up

Frozen embryo transfer (FET) was conducted when the patient had at least one euploid frozen blastocyst. The biopsied blastocyst was thawed using the Kitazato vitrification method. Three endometrial preparation protocols were involved in this study, including nature cycle, drug-induced ovulation cycle, and hormonal cycle. The hormonal cycle was utilized in most of women due to the flexibility of medication for thin endometrium and scheduling visit time. The nature cycle protocol was preferred for patients with secondary infertility who had normal menstrual patterns, while the drug-induced ovulation cycle protocol was favored for those with abnormal menstrual patterns. A single euploid blastocyst was transferred on day 5 or day 6 of progesterone administration, and the serum hCG concentration was measured 12 days later after the blastocyst transfer. Transvaginal ultrasonography was performed to confirm a gestational sac and a fetal heartbeat after two weeks. The follow-up continued until the baby was born.

Table 1 Baseline characteristics and stimulation cycle parameters of patients

	PPOS group (*n* = 299)	GnRH antagonist group (*n* = 299)	*P* value
Female age (year)	36.73 ± 5.19	36.70 ± 5.25	0.931
Male age (year)	39.41 ± 5.96	38.81 ± 6.28	0.227
BMI (kg/m2)	22.44 ± 2.80	22.32 ± 2.99	0.631
AMH (ng/ml)	3.86 ± 3.77	4.10 ± 3.78	0.444
bFSH (IU/L)	7.33 ± 2.71	7.03 ± 2.13	0.156
Indication for PGT-A			0.277
Advanced maternal age	90	104	
Recurrent miscarriage	126	129	
Repeated implantation failure	19	11	
Mixed	64	55	
Initial gonadotrophin dose (IU)	248.08 ± 63.27	236.20 ± 69.66	0.030*
Total gonadotrophin dose (IU)	2356.33 ± 715.93	2360 ± 851.41	0.952

*, $P < 0.05$

Statistical analysis

Propensity score matching (PSM) was performed to adjust for potential confounding factors, including female age, body mass index (BMI) and anti-Müllerian hormone (AMH) levels. The matching ratio of patients in the PPOS group to those in the GnRH antagonist group was 1:1. Continuous variables were expressed as mean ± SD, whereas categorical variables were presented as percentages. A t-test was utilized for quantitative variables and either the chi-square test or Fisher's exact test was employed to compare percentages. All statistical calculations were conducted in SPSS software (Version 26.0, IBM Corp, Armonk, NY).

Results

Baseline characteristics

A total of 681 patients who underwent a PPOS protocol and 493 who underwent a GnRH antagonist were enrolled. The incidence of failed triggers was 0.59% (4/681) in the PPOS group and 0.61% (3/493) in the GnRH antagonist group. After applying the inclusion and exclusion criteria, 419 patients in the PPOS group and 336 patients in the GnRH antagonist group were available for PMS analysis. Ultimately, 299 patients from the PPOS group were successfully matched with 299 patients from the GnRH antagonist group. Following PSM, no statistically significant difference was observed in baseline characteristics between PPOS group and GnRH antagonist group, including female age, Male age, BMI, AMH, total gonadotrophin dose, baseline FSH value, and indication rate of PGT-A, except for initial gonadotrophin dose (248.08 ± 63.27 vs. 236.20 ± 69.66, $P = 0.030$) (Table 1). Additionally, the incidence of moderate or severe ovarian hyperstimulation syndrome (OHSS) were 0.67% (2/299) and 1.00% (3/299) in PPOS group and GnRH antagonist group, respectively.

Embryo outcomes and genetic status

As shown in Table 2, the number of oocytes at retrieval per cycle was lower (12.70 ± 7.78 vs. 14.36 ± 8.63, $P = 0.013$) in the PPOS group compared to the GnRH antagonist group. Similarly, there were fewer MII oocytes (10.27 ± 6.49 vs. 11.60 ± 6.71, $P = 0.015$), two pronuclei zygotes (7.80 ± 4.91 vs. 8.90 ± 5.14, $P = 0.007$), and D3 good quality embryos (5.43 ± 3.79 vs. 6.37 ± 4.19, $P = 0.004$) in the PPOS group. However, no statistically significant differences were observed between the two groups regarding the number of biopsied blastocysts (3.51 ± 2.93 vs. 3.91 ± 3.19, $P = 0.116$) and the number of good-quality blastocysts (1.90 ± 2.24 vs. 2.22 ± 2.64, $P = 0.114$). The euploidy rate (43.3% vs. 45.0%, $P = 0.423$), aneuploidy rate (36.9% vs. 36.0%, $P = 0.127$), and mosaic rate (19.4% vs. 17.6%, $P = 0.127$) were comparable between the PPOS group and the GnRH antagonist group. Besides, the whole genome amplification (WGA) failure rate was lower in the PPOS group (0.4% vs. 1.4%, $P = 0.025$). Furthermore, multivariate linear regression analysis was conducted to assess the relationship between COH protocols and the number of oocytes retrieved (Table 3). The results indicated that the PPOS protocol might be linked to the number of oocytes, as the P value was 0.059. However, the PPOS protocol was not associated with other embryo outcomes based on the results of linear regression analysis (Supplementary Tables 1–5).

Pregnancy outcomes

A total of 485 FET cycles were conducted, and a single blastocyst transfer strategy was adopted for all FET cycles (Table 4). The rates of endometrial preparation protocol and endometrial thickness on the transfer day were not significantly different between the PPOS group and the GnRH antagonist group. Biochemical pregnancy rate (65.9% vs. 67.6%, $P = 0.772$), clinical pregnancy rate (58.1% vs. 59.8%, $P = 0.713$), implantation rate (58.1% vs. 59.8%, $P = 0.713$), and live birth rate (51.1% vs. 46.9%, $P = 0.364$) were comparable between the two groups. However, the miscarriage rate was higher in the GnRH antagonist group (9.0% vs. 19.0%, $P = 0.018$). Furthermore, the results of multivariate logistic regression analysis also supported that the PPOS protocol was associated with lower miscarriage rate (Odds Ratio = 0.423, 95% CI: 0.206–0.869) (Table 5) and not associated with other pregnancy outcomes (Supplementary Tables 6–8).

Genetic status of biopsied blastocyst across different age groups

To investigate whether PPOS protocol affects the genetic status of biopsied blastocysts across different age groups, we divided enrolled patients into four subgroups: 20 ~ 35 years old, 35 ~ 38 years old, 38 ~ 40 years old, and 40 ~ 45 years old. As shown in Fig. 1A, the euploidy rate

Table 2 Embryos outcomes of ovarian stimulation and PGT-A results

	PPOS group	GnRH antagonist group	*P* value
Oocytes at retrieval	12.70 ± 7.78	14.36 ± 8.63	0.013*
MII oocytes number	10.27 ± 6.59	11.60 ± 6.71	0.015*
Two pronuclei number	7.80 ± 4.91	8.90 ± 5.14	0.007*
D3 good quality embryo number	5.43 ± 3.79	6.37 ± 4.19	0.004*
Biopsied blastocyst number	3.51 ± 2.93	3.91 ± 3.19	0.116
good-quality blastocyst number	1.90 ± 2.24	2.22 ± 2.64	0.114
Euploid blastocyst rate (/biopsied blastocyst number)	43.3% (455/1050)	45.0% (526/1168)	0.423
Aneuploid blastocyst rate (/biopsied blastocyst number)	36.9% (387/1050)	36.0% (420/1168)	0.661
mosaic blastocyst rate (/biopsied blastocyst number)	19.4% (204/1050)	17.6% (206/1168)	0.127
WGA failure rate	0.4% (4/1050)	1.4% (16/1168)	0.025*

WGA, whole genome amplification; *, $P < 0.05$

Table 3 Multivariate linear regression analysis of the number of oocytes. ($R^2 = 0.447$)

Independent variable	β	t	*P* Value	95% CI for Exp(B)	
				lower	upper
Female age	-0.177	-3.222	0.001*	-0.453	-0.110
Male age	-0.026	-0.518	0.605	-0.173	0.101
COH protocol	0.063	1.893	0.059	-0.039	2.087
BMI	0.055	1.585	0.114	-0.037	0.347
AMH	0.392	8.743	0.000*	0.676	1.067
bFSH	-0.137	-3.924	0.000*	-0.692	-0.230
Initial gonadotrophin dose	-0.159	-2.445	0.015*	-0.036	-0.004
Total gonadotrophin dose	0.025	0.466	0.641	-0.001	0.001

*, $P < 0.05$

Table 4 Comparison of pregnancy outcomes in the PPOS group and the GnRH antagonist group

	PPOS group	GnRH antagonist group	*P* value
FET cycles	229	256	
Endometrial preparation			0.059
Natural cycles	15.7% (36/229)	23.0% (59/256)	
Drug-induced ovulation cycles	10.9% (25/229)	13.3% (34/256)	
Hormonal cycles	73.8% (169/229)	63.7% (163/256)	
Endometrial thickness (mm)	8.6 ± 1.8	8.7 ± 1.9	0.625
Biochemical pregnancy (%)	65.9% (151/229)	67.6% (173/256)	0.772
Clinical pregnancy (%)	58.1% (133/229)	59.8% (153/256)	0.713
Implantation rate (%)	58.1% (133/229)	59.8% (153/256)	0.713
Miscarriage rate (%)	7.9% (12/151)	16.8% (29/173)	0.019*
Live birth rate (%)	51.1% (117/229)	46.9% (120/256)	0.364

*, $P < 0.05$

Table 5 Multivariate logistic regression analysis of the miscarriage rate. ($R^2 = 0.059$)

Independent variable	β	Wald	*P* Value	Odds Ratio	Odds Ratio (95% CI)	
					lower	upper
Female age	-0.104	2.083	0.149	0.901	0.782	1.038
Male age	0.032	0.506	0.477	1.032	0.946	1.126
Infertility type						
primary infertility				1(ref)		
Secondary infertility	18.027	0.000	0.998	NA		
Indication for PGT-A						
advanced age				1(ref)		
recurrent miscarriage	0.507	0.377	0.539	1.661	0.329	8.388
repeated implantation failure	-17.997	0.000	0.998	NA		
Mixed	0.987	1.730	0.188	2.683	0.616	11.678
COH protocols						
GnRH antagonist				1(ref)		
PPOS	-0.861	5.484	0.019*	0.423	0.206	0.869
Endometrial preparation						
Natural cycles				1(ref)		
Drug-induced ovulation cycles	-0.034	0.002	0.961	0.967	0.253	3.697
Hormonal cycles	0.465	0.939	0.332	1.592	0.622	4.074
Endometrial thickness	-0.222	4.445	0.035*	0.801	0.652	0.985

NA, not applicable

*, $P < 0.05$

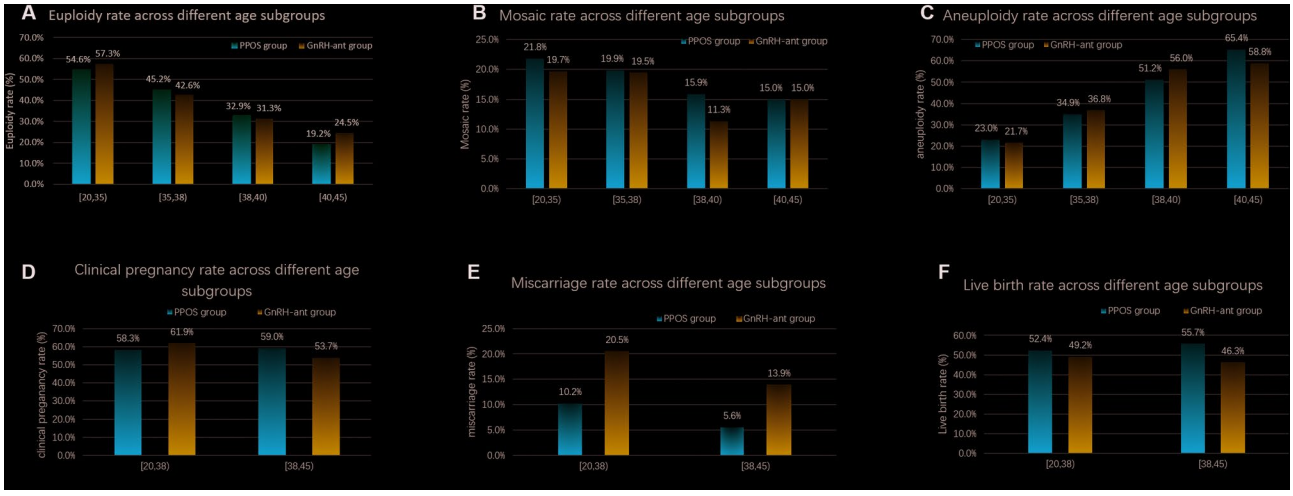

Fig. 1 Genetic status of biopsied blastocysts and pregnancy outcomes across different age subgroup of PPOS group and GnRH antagonist (GnRH-ant) group: euploidy rate (**A**), mosaic rate (**B**), aneuploidy rate (**C**), clinical pregnancy rate (**D**), miscarriage rate (**E**), and live birth rate (**F**)

decreased with increasing age in both the PPOS group and the GnRH antagonist group. The highest euploidy rate was 54.6% in 20–35 years old patients of the PPOS group and 57.3% in 20–35 years old patients of the GnRH antagonist group, respectively. However, no significant difference was detected in any age cohort between the PPOS group and the GnRH antagonist group. Meanwhile, the mosaic rate and aneuploidy rate between the PPOS group and the GnRH antagonist group were similar across all age subgroups (Fig. 1B and C).

Pregnancy outcomes in different age groups

We compared pregnancy outcomes in women under the age of 38 and women aged 38 and above between the PPOS group and the GnRH antagonist group (Fig. 1D-F). The clinical pregnancy rates in different age subgroups were comparable between the PPOS group and the GnRH antagonist group (< 38, 58.3% vs. 61.9%, $P = 0.517$; ≥38, 59.0% vs. 53.7%, $P = 0.595$). Live birth rates across all age subgroups were also similar between the two groups (< 38, 52.4% vs. 49.2%; ≥38, 55.7% vs. 46.3%). However, the miscarriage rate was lower in women under the age of 38 in the PPOS group (10.2% vs. 20.5%, $P = 0.041$). The

miscarriage rate was lower in women aged 38 and above in the PPOS group, although the difference was not significant (5.6% vs. 13.9%, $P = 0.429$).

Discussion

In this study, we demonstrated comparable euploidy rates of blastocysts in PGT-A cycles between the PPOS protocol and the GnRH antagonist protocol. Euploidy rates remain similar across different age subgroups within these two groups. Furthermore, pregnancy outcomes, including clinical pregnancy rate and live birth rate in FET cycles, were identical. However, the miscarriage rate in the PPOS group was lower than that in the GnRH antagonist group.

Several studies about PPOS have been conducted to investigate its administration and efficacy [4, 6]. First, the vast majority of prospective and retrospective IVF/ICSI studies [13–18] demonstrated no differences in retrieved outcomes between PPOS and GnRH antagonist protocols, including the number of oocytes, MII oocytes, fertilization rate, morphological score of D2-3 embryo, and viable blastocysts. However, a retrospective study including 1652 PGT-A cycles of social fertility preservation reported by Giles et al. [8] found that more oocytes were retrieved in PPOS protocol, while other retrieved outcomes were equivalent to those in GnRH antagonist protocol. The increased retrieved oocytes may be due to a higher total gonadotrophin dose in PPOS [8]. In another small sample retrospective cohort PGT-A study, a higher MII rate and fertilization rate, along with a lower blastocyst rate, were detected in the PPOS group, but the number of oocytes retrieved was similar between PPOS and GnRH antagonist groups [7]. In our study, we found an identical number of blastocysts but fewer oocytes, MII oocytes, two pronuclei zygotes, and D3 good-quality embryos in the PPOS group compared to the GnRH antagonist group. However, it should be noted that this difference might be resulted from lower AMH levels and higher baseline FSH levels in PPOS, although the difference was not significant. A higher initial gonadotrophin dose also suggested more women with decreased ovarian reserve in PPOS. A randomized controlled trial may be necessary, as the retrieved outcomes among these retrospective studies in PGT-A cycle were inconsistent.

Second, several studies have retrospectively compared euploid blastocyst rates between PPOS protocol and GnRH analog protocols [7–10, 19–21]. According to a recent retrospective cohort study, oocytes retrieved, MII oocytes, fertilized oocytes, and viable embryos were comparable between dydrogesterone and MPA when PPOS was applied in women with polycystic ovarian syndrome [22]. However, the euploid blastocyst rate between MPA and dydrogesterone remains unclear. In these studies using MPA, the euploid blastocyst rate was from 31.8 to 38.7% [7, 8, 19]. Our study showed a slightly higher euploidy rate of 43.3% when MPA was used in the PPOS protocol, which may be attributed to the younger female age in our study. In these studies using dydrogesterone in PPOS, two studies protocol showed similar euploidy rates of 34.88% [9] and 33.14% [21], while a higher euploidy rate of 46.5% was noted in Wang et al.'s study [20]. Above all, most studies showed a similar blastocyst euploidy rate between deydrogesterone and MPA.

On the other hand, the euploidy rate per biopsied blastocyst were comparable between PPOS and GnRH antagonist according to previous studies [8, 9, 19–21] and our study. In different age subgroups of PPOS and GnRH antagonist, both Yang et al.'s study [9] and our study showed no significant difference in euploidy rate. However, Pai et al. reported a lower euploidy rate in the elder subgroup (≥ 38-year-old) of the PPOS group [7]. The significant result from Pai et al.'s study [7] should be interpreted with caution, as only 19 PPOS cycles were enrolled in the elder subgroup. Wan et al. found a higher euploidy rate in women aged ≥ 35 years undergoing the PPOS protocol [10]. Additionally, the aneuploidy rate per biopsied blastocyst was lower in PPOS than in GnRH antagonist although the euploidy rate were similar according to the study by Giles et al. [8]. In this study by Giles et al., it should be noted that women in the ≤ 35 years subgroup undergoing PPOS protocol had a younger age than those with the GnRH antagonist protocol. In molecular testing, Oktem et al. found that exposure of antral follicles to MPA did not have any detrimental effects on steroidogenic, ovulatory, and luteal functions compared to GnRH antagonist cycles by analyzing luteinized mural granulosa cells [23]. Therefore, more good-quality studies are needed to confirm this question in the future, as all these studies were retrospective investigations.

Finally, pregnancy outcome is another indication for evaluating embryo quality from PPOS protocols. In the conventional IVF/ICSI, clinical pregnancy rates, miscarriage rates, and live birth or ongoing pregnancy rates were similar between PPOS and GnRH analogs according to a recent meta-analysis [24, 25]. Even in the women with decreased ovarian reserve or predicted suboptimal responders, MPA was considered a patient-friendly alternative to antagonists, as similar ovarian response and live birth rates were observed between the two groups [26, 27]. In this study, either clinical pregnancy rate or live birth rate was comparable in the PPOS group and GnRH antagonist group, which was consistent with previous studies in PGT-A groups [7–9, 19–21]. However, the miscarriage rate was lower in the PPOS group than GnRH antagonist group in both a large retrospective study by Giles et al. [8] and our study. In another two small sample studies [7, 20], the miscarriage rate was also higher in the GnRH antagonist group than the PPOS group, although

the difference was not significant. Therefore, the PPOS protocol seemed to yield a lower miscarriage rate than the GnRH antagonist protocol, as the clinical pregnancy rate and live birth rate were similar between these two protocols. A prospective randomized controlled study may be necessary to confirm this issue since all these studies were retrospective and the causes of miscarriage are highly complex.

Some limitations should be noted in the present study. First, this study was retrospective, non-randomized design. Although PSM and regression analysis were utilized to migrate bias from confounding factors, it may still influence the results. Some results from regression analysis should be interpreted with caution due to a low R^2 value. Second, the generalizability of this study should be approached with caution, as it was conducted at a single center. Additionally, the limitation from PGT-A testing method should be noted, particularly regarding mosaicism, even though the cut-off (30% ~ 70%) was applied in this study. Finally, the sample size was small, particularly since they were divided into different subgroups. Overall, it is crucial to further validate these results through multicenter prospective randomized controlled studies with a large sample size.

In conclusion, our finding provided further evidence that PPOS protocol seems to be an effective option for couples undergoing PGT-A, as the genetic status of biopsied blastocyst and main clinical pregnancy outcome did not change in patients with PPOS protocol. Additionally, a lower miscarriage rate in these patients should be noted as another potential advantage, although this needs to be confirmed by further studies.

Abbreviations

AMH	Anti-Müllerian hormone
ART	Assisted reproductive technology
BMI	Body mass index
COH	Controlled ovarian hyperstimulation
FET	Frozen embryo transfer
GnRH	Gonadotrophin releasing hormone
ICSI	Intracytoplasmic sperm injection
MPA	Medroxyprogesterone acetate
PGT-A	Preimplantation genetic testing for aneuploidy
PPOS	Progestin-primed ovarian stimulation
PSM	Propensity score matching

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12958-025-01398-9.

Supplementary Material 1

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Author contributions

Hu Tan, Fenghua Liu, and Xiqian Zhang contributed to the design of study. Hu Tan, Li Huang, Wenjuan Liu, and Jin Yan were involved in data analysis. Yujiang Wang, Li Li, Yuqiang Huang, and Zonghui Xiao engaged in the critical discussion of the draft. Hu Tan drafted this manuscript, while Xiqian Zhang and Fenghua Liu revised it. All authors critically reviewed and approved the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of the Guangdong Women and Children Hospital (No. 202401380).

Consent for publication

Informed consents for publication were obtained from all participants.

Competing interests

The authors declare no competing interests.

Clinical trial number

not applicable.

Author details

[1]Reproductive Medical Center, Guangdong Women and Children Hospital, Email address, Guangzhou 511400, Guangdong Province, China

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