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Comparison of the euploidy rate in preimplantation genetic testing for aneuploidy cycles following progestin-primed versus gonadotropin-releasing hormone antagonist protocol: a randomized controlled study

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Abstract

Background Progestins can block endogenous luteinizing hormone secretion from the pituitary gland and have shown similar efficacy in terms of collecting competent oocytes and embryos; however, some inconsistencies have been proposed by the previous papers regarding the quality of oocytes and embryos obtained with the use of progestins. This study aimed to compare the euploidy rate between women treated with progestin-primed ovarian stimulation (PPOS) and the gonadotropin-releasing hormone (GnRH) antagonist protocol.

Methods This is a prospective randomized study of 240 infertile women undergoing PGT-A between August 2021 and July 2023. Infertile women with advanced maternal age (38–45 years), recurrent pregnancy loss (≥ 2 or 3 consecutive miscarriages), and repeated implantation failure (≥ 4 embryos replaced or ≥ 2 blastocysts replaced without success) undergoing PGT-A cycles were included. Women were randomly assigned into the PPOS group ($n = 120$) or the antagonist group ($n = 120$) according to a computer-generated randomization list. Dydrogesterone 20 mg per day was given from the start of ovarian stimulation until the trigger day in the PPOS group. In the antagonist group, an antagonist 0.25 mg was given daily from the sixth day of ovarian stimulation until the trigger

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day. The primary outcome measure was the euploidy rate, defined as the number of euploid blastocysts per injected oocyte.

Results No significant differences were observed in the demographic and ovarian stimulation characteristics between the two groups. The euploidy rate was comparable between the PPOS and antagonist group (12.5% vs. 16.0% respectively, $P > 0.05$). No significant differences were observed between the two groups in positive pregnancy test, clinical pregnancy, miscarriage, ectopic pregnancy, or live birth rates per transfer in the first frozen embryo transfer cycles.

Conclusion Both PPOS and antagonist protocols had similar euploidy rates in PGT-A cycles.

Trial registration Clinicaltrials. gov identifier: NCT04989348 (https://www.clinicaltrials.gov/). Trial registration date: Clinicaltrials. gov: 30 July 2021.

Keywords Progestin-primed ovarian stimulation, Euploidy rate, Preimplantation genetic testing for aneuploidy, Live birth rate

Background

In vitro fertilization (IVF) involves multiple stages including ovarian stimulation, oocyte retrieval and embryo transfer after fertilization. Gonadotropin-releasing hormone (GnRH) agonists have been used in ovarian stimulation for IVF to prevent the luteinizing hormone (LH) surge and premature ovulation and are administered in the luteal phase of the preceding cycle or the follicular phase of the treatment cycle i.e. the agonist protocol. GnRH antagonists are more commonly used currently i.e. the antagonist protocol. In addition to the advantage of simplicity, antagonists are associated with a substantial reduction in ovarian hyperstimulation syndrome by allowing for agonist triggers with a shorter half life of physiologic LH without reducing the chance of achieving live birth when compared with the agonist protocols [1].

Progestins can inhibit the pituitary LH surge during ovarian stimulation and studies have demonstrated that progestin-primed ovarian stimulation (PPOS) effectively blocks the LH surge during ovarian stimulation for IVF [2–5]. The PPOS protocol is simpler and cheaper when compared with the antagonist protocol. Owing to its negative effects on the endometrium, fresh embryo transfer is not possible, and elective freezing of all embryos is required. The PPOS protocol is indicated for women who freeze all embryos for various reasons, including women with polycystic ovary syndrome, at risk of ovarian hyperstimulation, undergoing preimplantation genetic testing and oocyte freezing for fertility preservation.

A randomized trial comparing medroxyprogesterone and GnRH antagonists in an oocyte donation program demonstrated a similar number of mature oocytes but reported lower ongoing pregnancy and live birth rates in recipients of oocyte donors who had received medroxyprogesterone in IVF [6]. However, the oocyte recipients in the trial were not randomized. Another randomized trial with a similar design in oocyte donation demonstrated a similar number of oocytes obtained and comparable pregnancy outcomes of oocyte recipients when the oocyte donors were stimulated using PPOS or the antagonist protocol [7]. Therefore, the effect of the progestin used in IVF on pregnancy outcomes remains controversial. The PPOS protocol may adversely affect the euploidy rate of embryos, leading to a lower live birth rate.

The probability of having a live birth is mainly determined by the chromosomal status of the embryos [8]. Preimplantation genetic testing for aneuploidy (PGT-A) has been widely used in women with advanced age, recurrent pregnancy loss, or repeated implantation failure to improve the pregnancy outcomes [9]. As the turnaround time of PGT-A with next-generation sequencing is approximately a week, embryo transfer cannot be performed in the stimulated cycle. All blastocysts are vitrified following trophectoderm biopsy, and blastocysts with normal chromosomal number are replaced later. Several retrospective studies have reported that pregnancy outcomes of frozen embryo transfer (FET) following ovarian stimulation using the PPOS protocol have no negative effect on euploid blastocyst formation when compared with the antagonist protocol [10–12]. However, one retrospective study comparing PPOS protocol with the conventional GnRH antagonist approach found PPOS protocol could potentially reduce the euploidy rate in aging IVF patients (≥ 38 years old) [13]. Due to the retrospective nature of these studies, the results are to be interpreted with caution. Before the PPOS protocol is widely implemented, further randomized trial is needed to provide high quality evidence in this area.

This randomized trial aimed to compare the euploidy rates between the PPOS and antagonist protocols in women undergoing PGT-A. The hypothesis was that the PPOS protocol may result in a lower euploidy rate than the antagonist protocol.

Methods

Study population

This randomized study was conducted at the Shanghai First Maternity and Infant Hospital between August 2021

and July 2023. The etiologies of infertility in these women include tubal factors, ovulation dysfunction, endometriosis, unexplained and severe male factors. However, women with advanced maternal age and recurrent pregnancy loss may not have such clear cause of infertility. Consecutive women attending the Centre were screened and recruited if they fulfilled the selection criteria. The inclusion criteria were: (i) age of < 43 years at the time of ovarian stimulation for IVF; (ii) PGT-A performed for advanced maternal age (≥ 38 years), recurrent pregnancy loss (≥ 2 consecutive pregnancy loss), or repeated implantation failure (≥ 4 embryos replaced or ≥ 2 blastocysts replaced without success). Women were excluded if they had: (i) used donor eggs or sperm, (ii) hydrosalpinx on scanning and not treated, (iii) functional ovarian cyst with estradiol > 100 pg/mL, (iv) an abnormal chromosome in either or both partners, and (v) a congenital uterine anomaly.

All women were fully counseled and a written informed consent was signed before participation. They voluntarily participated in this study, and no monetary benefit was paid during recruitment. This study was approved by the Institutional Review Board of our hospital (No. KS23157) and registered at Clinicaltrials.gov (identifier NCT04989348).

Randomization

Before commencing ovarian stimulation, women were randomly assigned on the day of ovarian stimulation into one of two groups in a 1:1 ratio with blocks of 10 i.e. the PPOS group and the antagonist group. A randomization table was created using a computer application (www.randomization.com). Women and physicians could not be blinded while the biostatistician was blinded to the group assignment prior to the completion of the statistical analysis.

Ovarian stimulation

Women started ovarian stimulation using either the PPOS or GnRH antagonist protocols. In the PPOS group, on day 2–3 of the period, human menopausal gonadotropin (Lebaode, Lizhu, China) or recombinant basal follicle stimulating hormone (FSH, Gonal F, Merck Serono S.p.A, Modugno, Italy) was administered at 150–225 IU per day based on the antral follicle count, age of the woman, body mass index, and their previous ovarian response according to the standard operating procedure of the Centre. Dydrogesterone (20 mg/day; Abbott Biologicals B.V., the Netherlands) was administered on the same day and continued till the day of trigger. In the antagonist protocol, similar criteria for the starting dose and dosage adjustments were used, and 0.25 mg daily antagonist (Orgalutran, Organon, Dublin, Ireland) was administered from the sixth day of ovarian stimulation until the day of trigger.

The ovarian response was monitored using serial transvaginal scanning, with or without hormonal monitoring. Further dosage adjustments were based on ovarian response at the discretion of the clinicians in charge. When three leading follicles reached ≥ 18 mm in diameter, triptorelin (0.1 mg; Decapeptyl, Ferring Pharmaceuticals, Netherlands) and human chorionic gonadotropin (hCG 2000 IU or 5000 IU; Lizhu Pharmaceutical Trading Co., China) or Ovidrel 250 μg (Merck Serono S.p.A., Modugno, Italy) were administered to trigger final maturation of oocytes. Oocyte retrieval were performed under transvaginal ultrasound guidance 36 h after the trigger.

Fertilization, embryo evaluation, and blastocyst culture

Approximately 4 h after oocyte retrieval, intracytoplasmic sperm injection was performed. Oocytes were decoronated and checked for the presence of two pronuclei to confirm fertilization. Embryos were graded on day 3 after retrieval as grade one to grade six according to the evenness of each blastomere and the percentage of fragmentation [14]. Embryos with 6–8 cells and grade one or two were considered top quality embryos. All good embryos were cultured to blastocysts, which were vitrified on day 5 or 6 of the embryo culture. Blastocysts were graded according to the Gardner classification [15]. Blastocysts with either an inner cell mass or a trophectoderm score of B or higher were regarded as utilizable.

Preimplantation genetic testing for aneuploidy (PGT-A)

Trophectoderm biopsy was performed on utilizable blastocysts, and approximately five cells were aspirated gently through a zona pellucida opening created by a non-contact 1.48-μm diode laser (Saturn 5 ActiveTM, Cooper Surgical, Inc., CT, USA). The biopsied cells were subsequently washed three times in 1×phosphate buffered saline (PBS) (Life Technologies, NY, USA), transferred to a polymerase chain reaction tube containing 2.5 μL 1×PBS, and cryopreserved at -80 °C until analysis was performed. The samples were analyzed and interpreted in an accredited genetic laboratory using next generation sequencing-based VeriSeq PGS assay, following standard protocols and manufacturer's recommendations (Illumina Inc., San Diego, USA). The PGT-A report classified embryos as euploid, aneuploid, mosaic, or inconclusive. Only euploid embryos were transferred.

Vitrification of blastocysts and frozen embryo transfer

Utilizable blastocysts after trophectoderm biopsy were cryopreserved using a vitrification protocol. Details of the vitrification and warming procedures were described before [16]. Vitrification was performed with MediCult Vitrification Cooling (Origio, Denmark) using ethylene

glycol, propylene glycol, and sucrose as cryoprotectants. For the warming procedure following vitrification, the straw was cut, and the capillary was pulled out of the liquid nitrogen and immediately warmed individually using MediCult Vitrification Warming (Origio, Denmark). After warming, the embryos were transferred to a culture dish for evaluation and further embryo development.

Women in both groups underwent frozen embryo transfer at least one month after the stimulation cycle if they had at least one euploid blastocyst. Frozen embryo tranfers were performed in natural cycles for ovulatory women and clomiphene-induced or hormone-replacement cycles for either ovulatory or anovulatory women. Only one euploid blastocyst was transferred in the frozen embryo transfer cycle.

Follow-up and data collection

Urine pregnancy tests or blood hCG levels were checked approximately 2 weeks after transfer, and pelvic scanning was scheduled later to confirm an intrauterine pregnancy and assess the number of gestational sacs. Women were referred for antenatal care when the pregnancy reached 10 weeks. Miscarriages, ectopic births, and live births were recorded.

Outcomes measures

The primary outcome measure was the euploidy rate, defined as the number of euploid blastocysts per injected oocyte. Secondary outcome measures included the euploid blastocyst rate per woman, clinical pregnancy, miscarriage, ectopic pregnancy and live birth rates in the first frozen embryo transfer cycle. Number of retrieved oocytes, number of mature occytes, number of oocytes fertilized, fertilization rate, cleavage rate, number of blastocyst formation, blastocyst formation rate, number of cycles with no blastocyst for biopsy, number of cycles with no euploid blastocysts for transfer were also compared. A baby born alive at 22 weeks of gestation was classified as a live birth. Clinical pregnancy was defined as the presence of at least one gestational sac on ultrasonography at 6 weeks. Clinical miscarriage rate was defined as the number of miscarriages before 22 weeks divided by total number of clinical pregnancies.

Statistical analysis and sample size estimation

According to a previous study by La Marca et al. [17] and our retrospective study [11], we anticipated the euploidy rate of blastocysts per injected oocyte was about 17% with standard deviation of 26% using the antagonist protocol. We hypothesized a difference in the euploid rate of 5% between the PPOS versus antagonist groups, the sample size required would be 106 in each arm to give a power of 0.8 and type I error of 0.05. Allowing 10% drop-out, 240 women or 120 in each arm will be needed. (Sigmastat, Jandel Scientific, San Rafael, CA, USA).

The one-sample Kolmogorov–Smirnov test was used to test the normal distribution of continuous variables. Continuous variables were given as mean ± standard deviation if normally distributed and as median (interquartile range) if not normally distributed. Statistical comparisons were conducted according to the intention-to-treat and per protocol using Student's t-test, Mann–Whitney U-test for continuous variables, and chi-square test for categorical variables, where appropriate. A multivariate linear regression model adjusted for potential correlations was used to evaluate the association between the euploidy rate and the use of ovarian stimulation protocols. Statistical analyzes were performed using the Statistical Program for Social Sciences (SPSS Inc., Version 25.0, Chicago, IL, USA). The two-tailed value of $P < 0.05$ was considered statistically significant.

Results

Participant flow

Between August 2021 and August 2023, 290 women were screened and 50 were excluded, including 20 who did not meet the selection criteria and 30 who declined to participate. Thus, 240 women were recruited for this study and underwent ovarian stimulation: 120 women in the PPOS group and 120 women in the antagonist group. During the study period, 53 and 47 women in the PPOS and antagonist groups respectively completed their first frozen embryo transfer cycle. All women completed the follow-up period for the live birth outcome. A flowchart of the participants' enrollment is illustrated in Fig. 1.

Baseline characteristics and the ovarian stimulation cycle

The baseline characteristics of women in the two groups are summarized in Table 1. Age of women, age of husbands, body mass index of women, infertility duration, proportion of primary infertility, anti-Mullerian hormone (AMH) level, basal FSH/estradiol/LH/progesterone levels, antral follicle count and indications for PGT-A were comparable for the two groups.

No significant differences were observed in the starting dose of FSH, duration of stimulation, serum progesterone level on the trigger day, premature ovulation, number of oocytes retrieved, number of mature oocytes, mature occyte rate, number of oocytes fertilized, fertilization rate, cleavage rate, number of blastocysts formation and blastocysts formation rate between the two groups. However, the total dose of FSH was statistically significantly lower while serum estradiol and LH levels on the trigger day were statistically significantly higher in the PPOS group than the antagonist group (Table 2).

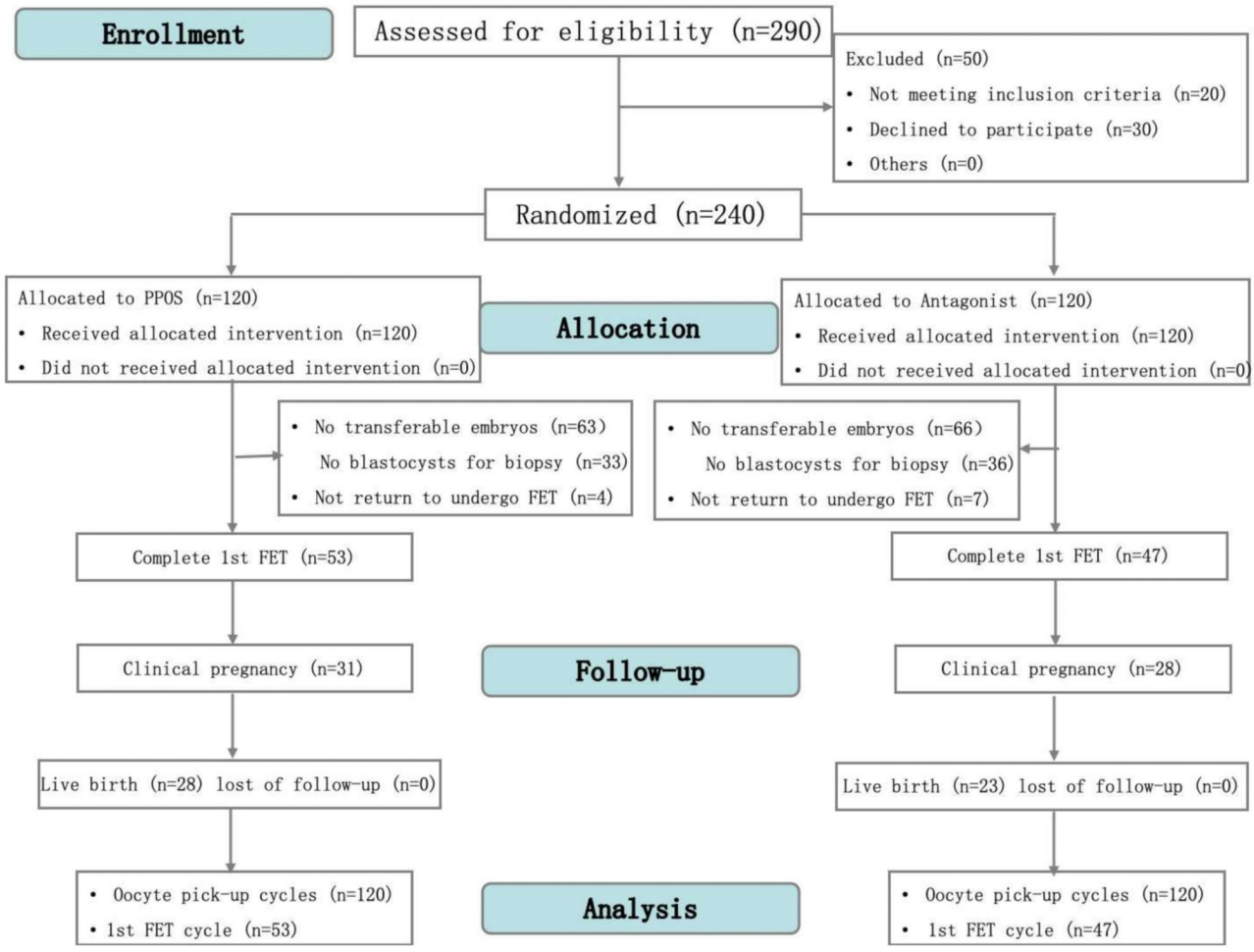

Fig. 1 Flowchart of the study

Table 1 Demographic characteristics of subjects in the study

Variables	PPOS group ($n=120$)	Antagonist group ($n=120$)	*P*-value
Age of women (years)	39.0 (35.3–41.0)	39.0 (34.0–42.0)	0.894
Age of husbands (years)	39.0 (34.3–43.0)	39.0 (34.0–43.0)	0.564
Body mass index of women (kg/m^2)	22.1 (20.5–23.6)	21.6 (20.0-23.6)	0.649
Primary infertility (%)	21.7 (26/120)	32.5 (39/120)	0.059
Infertility duration (years)	3.0 (1.0–5.0)	3.0 (1.5-5.0)	0.571
Serum AMH level (ng/ml)	2.2 (1.0-4.2)	1.9 (1.1–3.9)	0.637
Basal FSH level (IU/L)	7.1 (6.0-8.6)	7.2 (6.0-8.9)	0.887
Basal estradiol level (pg/ml)	42.7 (33.0-51.5)	37.8 (32.0-50.2)	0.245
Basal LH level (IU/L)	3.6 (2.6-5.0)	3.8 (2.8–4.8)	0.709
Basal progesterone level (ng/L)	0.6 (0.5–0.8)	0.6 (0.5–0.7)	0.517
Basal antral follicle count	10.0 (6.0–15.0)	9.0 (5.0–15.0)	0.157
Indication of PGT-A(%)			0.286
Advanced maternal age	45.0 (54/120)	45.8 (55/120)	
Recurrent pregnancy loss	18.3 (22/120)	16.7 (20/120)	
Repeated implantation failure	14.2 (17/120)	20.0 (24/120)	
Mixed	22.5 (27/120)	17.5 (21/120)	

Table 2 Characteristics of the stimulation cycle

Variables	PPOS group (*n* = 120)	Antagonist group (*n* = 120)	*P*-value
Starting dose of FSH (IU)	225.0 (225.0-225.0)	225.0 (225.0-225.0)	0.134
Total dosage of FSH (IU)	1800.0 (1575.0-2025.0)	1800.0 (1575.0-2212.5)	0.010
Duration of stimulation (days)	8.0 (7.0-8.8)	8.0 (7.0–9.0)	0.053
Serum estradiol level on trigger day (pg/ml)	1870.5 (912.7-2940.1)	1061.3 (592.0-2614.1)	0.007
Serum LH level on trigger day (IU/l)	4.3 (2.7–5.9)	2.4 (1.6–3.6)	0.000
Serum progesterone level on trigger day (ng/ml)	0.9 (0.6–1.2)	0.8 (0.6–1.2)	0.588
Premature ovulation (%)	0.8 (1/120)	0.8 (1/120)	1
No. of retrieved oocytes (n)	6.0 (3.0–10.0)	5.0 (3.0–10.0)	0.914
No. of mature occytes (n)	4.5 (2.0–8.0)	4.0 (3.0–9.0)	0.980
No. of oocytes fertilized (n)	3.0 (2.0–7.0)	3.0 (2.0–6.0)	0.728
Fertilization rate (%)	94.4 (75.0-100)	92.9 (75.0-100)	0.746
Cleavage rate (%)	100 (100–100)	100 (100–100)	0.648
No. of blastocysts formation (n)	1.5 (0–3.0)	1.0 (0–3.0)	0.422
Blastocysts formation rate (%)	59.4 (33.3–100)	50.0 (33.3–80)	0.299
Total No. of euploid blastocysts	93	97	
No. of euploid blastocysts (n)	0 (0–1.0)	0 (0–1.0)	0.995
Euploid blastocysts rate per injected oocyte (%)	12.5 (0–25.0)	16.0 (0-27.7)	0.477
Euploid blastocysts rate per woman (%)	33.3 (0-66.7)	50.0 (0-66.7)	0.459
No. of cycles with no blastocyst for biopsy (%)	27.5 (33/120)	30.0 (36/120)	0.669
No. of cycles with no euploid blastocysts for transfer (%)	52.5 (63/120)	55.0 (66/120)	0.698

Table 3 Comparison of pregnancy outcomes in the first frozen embryo transfer

	PPOS group (*n* = 53)	Antagonist group (*n* = 47)	*P*-value
Endometrial preparation, n (%)			0.995
Natural cycles	1.9 (1/53)	2.0% (1/47)	
Clomid-induced	11.5 (6/53)	10.0 (5/47)	
Hormonal cycles	83.0 (44/53)	91.5 (43/47)	
Endometrial thickness (day of trigger) (mm)	10.0 (8.6–11.0)	9.1 (8.5–10.4)	0.600
hCG test positive rate (%)	66.0 (35/53)	70.2 (33/47)	0.655
Clinical pregnancy rate (%)	58.5 (31/53)	59.6 (28/47)	0.912
Clinical miscarriage rate (%)	9.7 (3/31)	17.9 (5/28)	0.359
Ectopic pregnancy rate (%)	0 (0/35)	0 (0/33)	0
Live birth rate (%)	52.8 (28/53)	48.9 (23/47)	0.359

Primary and secondary outcomes

The euploid blastocyst rate per injected oocyte (12.5% vs. 16.0%) and per women (33.3% vs. 50.0%) was comparable between the PPOS and antagonist groups (Table 2).

The number of cycles with no blastocyst formation and with no transferable blastocysts (63 in the PPOS group and 66 in the antagonist group) did not differ significantly between the two groups.

A total of 100 women (53 and 47 women in the PPOS and antagonist groups respectively) had the first frozen embryo transfer with one euploid blastocyst replaced. During the study period, four women in the PPOS group and seven women in the antagonist group who had euploid blastocysts did not complete their first frozen embryo transfer cycle for personal reasons (divorce or busy schedule). The methods of endometrial preparation, endometrial thickness on the day of trigger, the positive pregnant test, clinical pregnancy rate, miscarriage rate, ectopic pregnancy rate and the live birth rates were similar between the two groups (Table 3).

Multivariate linear regression and subgroup analysis

The multivariate linear regression model using "backward conditional method" with variables including age of women, age of husbands, body mass index, primary infertility, infertility duration, AMH, basal FSH level, antral follicle count, indication of PGT-A, ovarian stimulation protocol, serum estradiol/LH/progesterone levels on the trigger day, total FSH dosage, duration of stimulation, number of oocytes retrieved, fertilization rate, cleavage rate and blastocysts formation rate revealed that only repeated implantation failure in the indication of PGT-A compared to the reference group, but not the ovarian stimulation protocol ($P = 0.277$), was associated with the euploidy rate of blastocysts per injected oocyte (Supplemental Table 1).

A subgroup analysis was performed by stratifying women according to the three indications for PGT-A (advanced maternal age, recurrent pregnancy loss, and repeated implantation failure). The euploidy rate of blastocysts per injected oocyte/biopsy (per woman), the clinical pregnancy rate and the live birth ratese were also comparable between the two groups (Supplemental Fig. 1).

Discussion

To our knowledge, this is the first randomized controlled trial to compare the euploidy rate of blastocysts between the PPOS and antagonist protocols in women undergoing PGT-A. We demonstrated similar euploidy rates of blastocysts in the PGT-A cycles using the PPOS and antagonist protocols. Moreover, the live birth rate of the first frozen embryo transfer cycle in those women who had euploid blastocysts in both groups were comparable.

Our study demonstrated that the total number of blastocysts, number of euploid blastocysts, and euploidy rate per injected oocyte or women were similar between the PPOS and antagonist protocols. These results suggested that the PPOS protocol has no adverse impact on embryo quality, at least when assessed by analyzing the chromosomes of the embryo. Our results are consistent with those of La Marca et al. [17], which demonstrated that the rate of euploid formation per injected oocyte was similar in women using either the PPOS protocol or the antagonist protocol during ovarian stimulation for IVF. However, only 48 women were recruited in the PPOS group in that study, which was an age-matched historical case-control study rather than a cohort study based on their study design. Notably, pregnancy outcomes after frozen embryo tranfer have not been reported. Other retrospective studies have demonstrated that the PPOS protocol has no negative effect on the formation of euploid blastocysts, and pregnancy outcomes in frozen embryo transfer cycles using the PPOS protocol were similar to those of the antagonist protocols [10–12]. The euploidy rate of blastocysts in the PPOS cycles may indicate that the live birth rate of PPOS is not inferior to that of ovarian stimulation using an antagonist [17, 18].

Our results indicated that progestins were capable of effectively preventing premature ovulation in PGT-A cycles; however, both the LH level and the estrogen level on the trigger day were significantly lower in the antagonist groups when compared with the PPOS group, suggesting the effect of pituitary suppression in the PPOS protocol may be weaker than that of the antagonist. In this study, the numbers of oocytes obtained and fertilized oocytes were similar in both the PPOS and antagonist groups. These results are consistent with those of previous studies that revealed comparable embryological characteristics between progestin and short agonist cycles [19, 20]. Studies on frozen embryo transfer cycles provide an opportunity to assess different protocols for oocyte quality and subsequent embryo development potential. While most researchers agree that elevated progesterone levels on trigger day do not have a negative impact on the frozen embryo transfer results of stimulated cycles using the PPOS protocol [2, 3, 21, 22], some have reported a negative effect of elevated progesterone on oocyte quality [23, 24]. In the first frozen embryo transfer cycle, we observed similar live birth rates in the PPOS and antagonist groups, and another RCT conducted by our group found comparable live birth rates of the first frozen embryo transfer following the PPOS and the antagonist protocol in women with an anticipated high ovarian response [25], these results indicated that the progestin used in the PPOS group was unlikely to be harmful to oocytes or embryos when compared with those of the antagonist group.

The advantages of progestins include oral administration and easier access [26]. PPOS is also more user-friendly, as fewer injections are required, and progestins are much cheaper than antagonists [6]. However, according to Ata et al. [18, 27], PPOS combined with an elective freeze-all approach may not be justified for all IVF cycles because avoiding fresh embryo transfer does not appear beneficial in the absence of a medical indication when fresh embryo transfer is not intended. In the PPOS protocol, freezing of all embryos and delayed transfer are mandatory. In cases where fresh embryo transfer is not required, such as fertility preservation, oocyte donation, or PGT, the PPOS protocol may be recommended as a first choice for suppressing premature ovulation [4]. Therefore, the potentially harmful effects of the hormonal environment on endometrial receptivity are avoided. Others who can benefit from the PPOS protocol are those at risk of ovarian hyperstimulation syndrome, because for these women, the application of the 'freeze-all' strategy and triggering can be exerted by the GnRH agonist, which helps to avoid early onset ovarian hyperstimulation syndrome [28].

The major limitation of the present study is use of the euploidy rate per injected oocyte as the primary outcome but the unit of randomization is per women, because we were concerned probably higher level of drop-out rate (about 30% of cycles with no blastocysts for biopsy in both groups) if the euploidy rate per woman was used to calculate the sample size. There are some factors other than euploid blastocyst formation may affect the euploidy rate per injected oocyte: oocytes fertilization rate, embryo cleavage rate and blastocysts formation rate, however, no difference were found in these rates between two groups and we included the euploidy rate per women as one of the secondary outcomes, which was also comparable between the PPOS and antagonist protocol. Another limitation was the relatively small sample size as we aimed to detect a 5% difference in the euploid per injected oocyte, only 120 women were recruited in each group. Many women had no transferable blastocysts; thus, less than half of the women in both groups completed their first frozen embryo transfer cycle. Therefore, pregnancy outcomes should be interpreted with caution. The third limitation was the recruitment of women with indications for PGT-A only; hence, our results may not

be extrapolated to the general population seeking IVF treatment, who may be younger, undergoing the first cycle, or have no history of miscarriage.

In conclusion, both PPOS and antagonist protocols had similar euploidy rates in PGT-A cycles.

Abbreviations

IVF	In vitro fertilization
GnRH	Gonadotropin-releasing hormone
LH	Luteinizing hormone
PPOS	Progestin-primed ovarian stimulation
PGT-A	Preimplantation genetic testing for aneuploidy
FET	Frozen embryo transfer
AMH	Anti-Müllerian hormone
FSH	Follicle stimulating hormone

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12958-025-01404-0.

Supplementary Material 1

Supplementary Material 2

Author contributions

L.W. and J.Y.W. was involved in study design, execution, analysis, manuscript drafting, critical discussion and final approval of the manuscript. Y.Z., C.Q. and X.H.W. were involved in study execution and critical discussion of the manuscript. E.H.Y.N. was involved in critical discussion and revision of the manuscript. A.A. and Z.Q.C. were involved in study design, supervising, coordinating and final approval of the manuscript. All authors read and approved the final 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 Shanghai First Maternity and Infant Hospital (KS23157). Informed consent was obtained from all patients. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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