Comparison of Cumulative Live Birth Rates Per Aspiration IVF/ICSI Cycle Between GnRH Antagonist Protocol and Progesterone-Primed Ovarian Stimulation Protocol for Infertility With Normal Ovarian Reserve: A Randomised Controlled Trial

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Research

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Abstract

Background: Oral progestin has been used to prevent premature ovulation during follicle stimulation protocols performed in combination with a freeze-only strategy. However, no studies have determined how oral progestin clinically compares to gonadotropin-releasing hormone (GnRH) antagonists in women with normal ovulation. This study aimed to compare the efficacy and safety of controlled ovarian stimulation between progestin-primed ovarian stimulation (PPOS) protocol and GnRH antagonist (GnRH-ant) protocol.

Methods: Young women with infertility and normal ovarian reserve who underwent in vitro fertilisation (IVF) treatments were screened and randomly allocated to the PPOS or GnRH-ant group. Women in the PPOS group underwent freeze-all and delayed embryo transfer, whilst fresh embryo transfer was preferred for those in the GnRH-ant group. The primary endpoint was the cumulative live birth rate (CLBR). Secondary endpoints included the incidence of premature luteinising hormone (LH) surge and the number of viable embryos.

Results: CLBRs were similar in the PPOS and GnRH-ant group (55.75% vs. 52.87%, respectively, $P > 0.05$). No premature LH surge was observed during ovarian stimulation in the PPOS group, although six (3.45%) cases were observed in the GnRH-ant group. On the trigger day, LH level was lower in the PPOS group than in the GnRH-ant group (2.30 ± 1.78 mIU/ml vs. 3.66 ± 3.52 mIU/ml, $P < 0.01$). There were no differences in the number of retrieved oocytes, mature oocytes, or viable embryos between the two groups. Other clinical outcomes including implantation rates (37.27% vs. 36.77%), clinical pregnancy rates (55.75% vs. 55.89%), and miscarriage rates (12.28% vs. 13.76%) were comparable between the PPOS group and GnRH-ant group ($P > 0.05$). There was also no significant differences in newborn weights for singleton or twin births between the two groups ($P > 0.05$).

Conclusion: Live birth outcomes are similar for PPOS and GnRH antagonist protocols in women with normal ovarian reserve. PPOS is likely to play a promising role in the freeze-only strategy given its simplicity and convenience for the patient.

Trial registration: This trial was registered in the China Clinical Trial Registry on September 6, 2018 (number: ChiCTR1800018246).

Background

In vitro fertilisation (IVF) is a widely used and effective treatment for infertility. The first and critical step for IVF or intracytoplasmic sperm injection (ICSI) is controlled ovarian hyperstimulation (COH). Luteinising hormone (LH) surge and ovarian hyperstimulation syndrome (OHSS), which result from multi-follicular development and high oestradiol levels, have always been the focus of various COH protocols. Gonadotropin-releasing hormone (GnRH) agonists and antagonists were introduced into COH protocols to prevent the premature elevation of endogenous LH to obtain good-quality embryos [1].

Within several hours, GnRH antagonists can directly inhibit gonadotrophin release without any initial flare-up effects by competitively binding to GnRH receptors in the pituitary [2]. This property allows GnRH antagonists to be used in the late follicular phase. In addition to being more cost effective, GnRH antagonists are associated with better patient acceptance and shorter gonadotropin duration than GnRH agonists. Additionally, rates of perimenopausal symptoms associated with low oestrogen levels are lower for GnRH antagonists than for GnRH agonists, and use of short-lived GnRH agonists to trigger final oocyte maturation rather than human chorionic gonadotropin (hCG) can effectively prevent OHSS [3]. The GnRH antagonist protocol (GnRH-ant) has been proven to effectively block premature pituitary LH secretion during COS [4]. It has been the first choice of COS in patients with normal ovulation [5] and those with polycystic ovary syndrome (PCOS) [6].

Pregnancy outcomes have improved with progress in embryo vitrification techniques, which may be associated with improved endometrial receptivity [7]. Progesterone-primed ovarian stimulation (PPOS) has been adopted as an innovative regimen for ovarian stimulation. Studies have demonstrated that PPOS is effective for suppressing premature LH surge and decreasing OHSS incidence when used in combination with a freeze-all strategy and a GnRH-agonist trigger [8]. Several randomised controlled trials (RCTs) have compared the number of oocytes retrieved and pregnancy outcomes, including clinical pregnancy and live birth rate, between progestin-mediated and GnRH antagonist protocols in patients with PCOS [9, 10] and poor responders [11]. Although these trials have reported no significant differences between the protocols, RCT data regarding the use of PPOS in patients with infertility who have normal ovarian reserve are limited. Therefore, in this prospective single-centre randomised controlled trial, we aimed to explore the differences between PPOS and GnRH antagonist treatment during COS in patients with normal ovulation. To achieve this aim, we evaluated the efficacy of ovarian stimulation based on the cumulative live birth rate (CLBR).

Methods

Study setting and allocation of patients

This prospective RCT was conducted at the reproductive centre of Shanghai East Hospital affiliated with Shanghai Tongji University School of Medicine between September 20, 2018, and December 31, 2019. This study was performed in accordance with the Declaration of Helsinki for medical research and Good Clinical Practice guidelines and was approved by the Ethics Committee of the Institutional Review Board (IRB) of the clinic (number: 2018-17). This trial was registered in the China Clinical Trial Registry on September 6, 2018 (number: ChiCTR1800018246). Written informed consent was obtained from all enrolled patients with infertility undergoing their first ovarian stimulation cycle.

The inclusion criteria were as follows: female age 22–40 years, spontaneous menstrual cycle (25–35 days), serum anti-Müllerian hormone (AMH) levels greater than 1.1 ng/ml, and first cycle of IVF or ICSI procedure. Exclusion criteria were endometriosis grade 3 or higher, basal oestradiol levels above 80 pg/ml, recurrent miscarriage, and any contraindications for COH.

A computer-generated list was used for randomisation. Patients who met the eligibility criteria were randomly allocated to each group via numbered sealed envelopes at a ratio of 1:1. A physician assigned the drugs according to the code, and an experienced nurse instructed the patients on how to use the drugs. Physicians, nurses, and embryologists were not blinded to allocation. A total of 348 women (174 in each group) were enrolled in this study.

PPOS protocol

On the second or third day of the menstrual period, transvaginal ultrasonography and basal serum hormone (follicle-stimulating hormone [FSH], LH, oestradiol [E2], and progesterone) levels were monitored to exclude any patients with cysts or elevated basal oestradiol levels. Tablets containing 10 mg oral medroxyprogesterone acetate (MPA, Shanghai Xinyi Pharmaceutical Co., China) and 150–225 (IU) of intramuscular human menopausal gonadotropin (hMG, Anhui Fengyuan Pharmaceutical Co., China) were administered daily starting from day 2 or 3 of the menstrual cycle (MC). The hMG dosage was adjusted according to serum E2 levels and follicle sizes. When three or more dominant follicles reached 18 mm in diameter, a double trigger was administered for final oocyte maturation. Subcutaneous (SC) GnRH agonist (0.1 mg triptorelin, Decapeptyl®; Ferring Pharmaceuticals, Germany) and intramuscular (IM) hCG (5,000 IU) injections were administered for final oocyte maturation. Oocyte retrieval was performed 36 h after administering the trigger.

GnRH antagonist (GnRH-ant) protocol

Participants receiving the flexible GnRH-ant protocol received daily injections of hMG (150–225 IU) from MC day 2–3 until the trigger day. The GnRH antagonist (Cetrotide, 0.25 mg, Merck-Serono) was administered when a rise in serum LH occurred or when leading follicular diameter >14 mm was observed. The dosage of hMG was adjusted according to the patient's characteristics, serum LH level, and follicular response. Similarly, final oocyte maturation was performed using the double trigger, and oocyte retrieval was performed approximately 36 h later.

Oocyte collection and embryo culture

Oocyte retrieval was performed in accordance with the routine protocol, and all follicles > 10 mm in diameter were aspirated. Standard insemination or ICSI was performed within 6 h of retrieval. On the third day, embryos were examined for the number and regularity of blastomeres and the degree of embryonic fragmentation. If available, up to two top-quality embryos were transferred on the third day in the GnRH-ant group if the patient's condition permitted fresh embryo transfer (low OHSS risk and optimal endometrium). The remaining top-quality embryos were frozen by vitrification, and the non-top-quality embryos were subjected to extended culturation. Only good morphological blastocysts were frozen on day 5 or day 6. In the PPOS group, all top-quality cleavage embryos were frozen on the third day, and the non-top-quality embryos were extensively cultured and cryopreserved using the Gardner and Schoolcraft system [12]. The viable embryos included all top-quality cleavage embryos (including grade I and grade II, 8-cell blastomere embryos) and good morphological blastocysts [12, 13].

Endometrium preparation and frozen embryo transfer

All patients in the PPOS group underwent frozen embryo transfer (FET). In the GnRH-ant group, freeze-all procedures were performed only in patients with a high risk of OHSS, a serum P level on trigger day exceeding 1.5 ng/ml, or based on personal choice. FET was conducted during the second menstrual cycle after the oocyte pickup (OPU) cycle. The methods for endometrial preparation in FET cycles were natural cycle, mild stimulation, and hormone replacement treatment (HRT), and the choice was based on routine procedures used in our clinic and in previous articles [14]. Briefly, the natural cycle was selected first for women with normal ovulation. HRT was preferred in patients with thin endometria. Oral and vaginal progesterone were simultaneously used for luteal support. When pregnancy was achieved, exogenous progesterone supplementation was continued until 10 weeks of gestation.

Outcome measures and definitions

The primary outcome measure was the CLBR. Secondary outcome measures included the number of oocytes retrieved, the incidence of premature LH surge, the duration and dosage of hMG treatment, numbers of mature oocytes and viable embryos, and rates of implantation and clinical pregnancy. Safety measurements included serious adverse events, such as moderate/severe OHSS, bleeding, and infection after oocyte retrieval. A completed OPU cycle was defined as one in which all embryos had been used or a live birth had been achieved. Low and high ovarian responses were defined as < 5 or > 15 retrieved oocytes, respectively. The implantation rate was defined as the number of gestational sacs visualised on ultrasound examination divided by the number of embryos transferred. Biochemical pregnancy was defined as serum β-hCG level ≥ 5 IU/l 2 weeks after embryo transfer. Clinical pregnancy was defined as at least one gestational sac on ultrasound 4 weeks after embryo transfer. The CLBR was calculated as the delivery of a living newborn after the 24^{th} gestational week divided by the number of enrolled patients. A premature LH surge during COH was defined as a serum LH level > 15 IU/l accompanied by an increase in progesterone. The OHSS was classified into three grades (mild, moderate, and severe) according to the 2016 guidelines [15].

Sample size

This was a prospective non-inferiority trial. In line with previous studies, the CLBR was 35% in the GnRH-ant protocol [16]. This study was powered to detect a significant difference of 15% in the CLBR. A sample size of 167 patients in each group was estimated to achieve at least 80% power to establish superiority at the 5% level of significance (PASS, version 11, NCSS, WI, USA). Given the possibility of a 5% dropout rate, we designed the study to include a total of 174 patients in each group.

Statistical analysis

The normality of the data distribution was assessed using the Shapiro–Wilk test. Continuous data are presented as the mean ± standard deviation (SD), while categorical data are presented as numbers and percentages. The results were compared between the two groups using unpaired Student's t-tests, Mann–

Whitney nonparametric U-tests, Pearson's chi-square tests, or Fisher's exact tests. A two-sided P value of < 0.05 was considered statistically significant. All data were analysed using the Statistical Package for the Social Sciences for Windows (SPSS, version 25.0, Chicago, IL, USA).

Results

Participant characteristics

Figure 1 shows the flowchart of the study. A total of 348 women meeting the eligibility criteria were randomly assigned to the PPOS and GnRH-ant groups. All patients in each group completed the oocyte retrieval process. Failure to obtain oocytes occurred in one patient in the PPOS group and no patients in the GnRH antagonist group. Four patients in the PPOS group and two patients in the GnRH-ant group had no viable embryos. Over the next 2 years, 170 patients in the PPOS group completed 200 FET cycles. 80 fresh embryo transfer cycles and 82 FET cycles were performed in the GnRH-ant group, in which 17 women underwent both fresh embryo transfer and FET cycles. Both groups included patients who did not undergo embryo transfer (32 in the PPOS group and 29 in the GnRH-ant group). The reasons for avoiding fresh embryo transfer in 63 patients were as follows: patient choice, high serum progesterone levels on the day of hCG administration, and risk of OHSS. Finally, 97 and 92 live births were recorded in the PPOS and GnRH-ant groups, respectively.

The general characteristics of the patients are shown in **Table 1**. No significant differences in age, body mass index (BMI), duration of infertility, antral follicle count (AFC), AMH levels, or basal hormone levels (FSH, LH, E2, and progesterone) were observed between the two groups (P > 0.05). There were also no significant differences in infertility factors between the groups (P > 0.05).

Ovarian stimulation, embryo outcomes, and hormonal profile

Table 2 shows the clinical outcomes of COH treatment in both groups. The duration of GnRH-ant treatment was 3.41 ± 1.77 days (1–9 days) in the GnRH-ant group. The dose and duration of MPA treatment in the PPOS group were 64.77 ± 28.96 mg (16–130 mg) and 8.79 ± 1.5 days (4–14 days), respectively. The dose of hMG was comparable between the groups (PPOS: 1,909.05 ± 421.77 IU vs. GnRH-ant: 1,828.88 ± 503.77 IU, P > 0.05), whereas the duration of stimulation was longer in the PPOS group (PPOS: 9.03 ± 1.56 days vs. GnRH-ant: 8.64 ± 1.75 days, P < 0.05). The PPOS protocol yielded a similar number of oocytes, metaphase II stage oocytes, and viable embryos when compared with the GnRH-ant protocol (PPOS: 9.88 ± 5.31 vs. GnRH-ant 9.14 ± 5.12; PPOS: 8.13 ± 4.66 vs. GnRH-ant: 7.49 ± 4.23; PPOS: 4.60 ± 2.58 vs. GnRH-ant: 4.44 ± 2.03, respectively, P > 0.05). Likewise, the rate of oocytes retrieved was similar in the two groups (PPOS: 82.69% vs. GnRH-ant: 83.34%, P > 0.05). The ultimate proportion of viable embryos per oocyte was also similar between the two groups (PPOS: 46.95% vs. GnRH-ant: 48.59%, P > 0.05). Dysfunctions in oocyte maturation occurred in three patients in the GnRH-ant group and no patients in the PPOS group.

The mean LH level on the trigger day was significantly lower in the PPOS group than in the GnRH-ant group (PPOS: 2.30 ± 1.78 mIU/ml vs. GnRH-ant: 3.66 ± 3.52 mIU/ml, respectively, P < 0.01), as was the progesterone level (PPOS: 0.74 ± 0.41 ng/ml vs. GnRH-ant: 0.99 ± 0.63 ng/ml, P < 0.01). However, the progesterone value on the day after trigger administration was similar between the two groups (PPOS: 3.8 ± 1.91 ng/ml vs. 4.17 ± 2.39 ng/ml. P > 0.05). No cases of LH surge were observed in the PPOS group, whereas six cases of premature LH surge occurred in the GnRH-ant group (range: 15.05–22.70 mIU/ml) on the trigger day. However, all patients eventually produced viable embryos (range: 2–11). Three patients in the PPOS group and 10 patients in the GnRH-ant group had LH levels >10 mIU/ml.

Pregnancy outcomes following frozen-thawed and fresh embryo transfer

Table 3 illustrates pregnancy outcomes in the two groups. During the study period, the PPOS group completed 200 FET cycles, while the GnRH-ant group completed 195 cycles (including 85 fresh embryo cycles and 110 FET cycles). The CLBR did not significantly differ between the PPOS group and the GnRH-ant group (55.75% vs. 52.87%, respectively, P > 0.05). The implantation, biochemical pregnancy, and clinical pregnancy rates were also comparable between the groups (PPOS: 37.27% vs. GnRH-ant: 36.77%; PPOS: 64% vs. GnRH-ant: 63.59%; PPOS: 55.75% vs. GnRH-ant: 55.89%, respectively, P > 0.05). There were no differences in the miscarriage rate (PPOS: 12.28% vs. GnRH-ant: 13.76%, P < 0.01). Two cases of ectopic pregnancy occurred in the PPOS group, while one case occurred in the GnRH-ant group. There were no statistically significant differences in the birth weights of singleton and twin newborns between the two groups (P > 0.05).

Table 4 shows that pregnancy outcomes following fresh embryo transfer and FET were similar in the GnRH-ant group, and that there were no significant differences in the birth weights of singleton and twin newborns. For fresh cycles, all of the transferred embryos were cleavage embryos, and both cleavage embryos and blastocysts were transferred for FET cycles. The rate of single embryo transfer was greater for fresh cycles than for FET cycles (26.25% vs. 8.7%).

Ovarian response and CLBR

Differences in ovarian responses to the two ovarian stimulation protocols are shown in **Figure 2**. Both protocols yielded low percentages of low and high ovarian response in women with normal ovulation, and the normal ovarian response accounted for the largest proportion of cases (PPOS: 68.96% [120/174] vs. GnRH-ant: 73% [127/174]). **Table 5** shows the endpoint CLBR in patients with low and high ovarian response in the two groups. In both groups, nine live births occurred in patients with low ovarian response. Seventeen (17/29) live births occurred in the PPOS group, while nine live births (9/17) occurred in GnRH-ant group.

Safety

No serious adverse events including moderate/severe OHSS, bleeding, and infection were observed among the participants in either group.

Discussion

Since CLBR was first proposed for evaluating the success of IVF in 1992 [17], an increasing number of researchers consider CLBR to be a good endpoint with which to evaluate the safety and efficacy of different ovarian stimulation protocols performing in conjunction with advanced cryopreservation. However, over the past two decades, there has been no consensus on the definition of CLBR [18]. Therefore, we calculated the CLBR over a 2-year period using the number of enrolled patients as the denominator. Previous studies have reported a comparable CLBR for PPOS and GnRH-ant in poor responders [11] and women with PCOS [10]. However, few RCT studies have explored differences in the CLBR between these two protocols in women with normal ovulatory infertility. In this trial, we investigated differences in the CLBR between PPOS and GnRH antagonist protocols during COS in patients with normal ovulation. Consistent with previous retrospective results, our finding indicated that the GnRH-ant and PPOS protocols had a similar CLBR in young women with infertility.

In the current study, similar oocyte yields, metaphase II oocyte numbers, implantation rates, and clinical pregnancy rates were obtained in the PPOS and GnRH-ant groups. Several studies have also noted similar embryonic and pregnancy outcomes (e.g., oocyte and embryo quality) for PPOS and ovarian stimulation protocols other than GnRH-ant [19, 20]. Moreover, there have been no differences in miscarriage rates or the euploidy rates of blastocysts between PPOS and GnRH-ant protocols [21]. This raises the question of whether application of progestin in ovarian stimulation protocols has entered a new era due to its oral convenience, the stability of LH levels, and good embryonic potential [22]. Further research is required to answer this question, and to confirm the efficacy and safety of the PPOS protocol.

A potential advantage associated with the freeze-all technique is that it may provide a more physiological hormonal and endometrial environment [23]. Zaca et al. [24] reported superior CLBR outcomes using frozen blastocyst transfer in the FET cycle. Our embryo transfer strategy was different for the GnRH-ant protocol, as we first chose cleavage embryo transfer for fresh cycles, using blastocyst transfer for FET cycles when fresh cycles failed. Eventually, no blastocysts were transferred, and the rate of single embryo transfer was higher for fresh cycles than for FET cycles in patients who had only one good-quality cleavage embryo for embryo transfer. However, the live birth rate was similar between the freeze-all strategy in the PPOS group and initial ET followed by frozen embryo replacement in the GnRH-ant group. This has been confirmed in several recent studies [25, 26]. Therefore, whether the freeze-all strategy is suitable for all normal ovarian responders remains controversial [27, 28].

We reported six cases of premature LH surge in the GnRH-ant group, yet none in the PPOS group, and the LH level on the trigger day was higher in the GnRH-ant group than in the PPOS group. Moreover, increases in LH levels were accompanied by increases in progesterone levels. These findings suggest that, although both GnRH antagonists and PPOS are non-down-regulating ovarian stimulation protocols, the mechanism by which LH suppression occurs using progestin differs from that using GnRH antagonists. Studies in animal models have shown that progesterone-mediated suppression of LH surge is mediating by hypothalamic dynorphin and gamma-aminobutyric acid (GABA) receptor signalling and kisspeptin [29,

30], whereby serum LH levels decline slowly and steadily during PPOS. In contrast, GnRH antagonist-mediated pituitary secretion occurs rapidly due to direct and competitive blockade of GnRH receptors in the late follicular phase. The competitive nature of pituitary suppression may be the reason for occasional escape. Although LH surge was observed in six patients, the flexible advanced arrangement of oocyte retrieval allowed us to obtain oocytes and viable embryos in these patients [31, 32].

To date, there is no consensus regarding the definition of LH surge, though it is widely defined as an elevated LH value accompanied by a decline in E2 and increased progesterone levels. However, due to wide individual variations, there have been no reports in the published literature of a specific cut-off level for LH surges. Although the cut-off value for LH surge differs among centres, pregnancy outcomes do not appear to be affected in the FET cycle; however, a previous study reported decreased probability of pregnancy outcomes due to increases in endogenous progesterone on the hCG day [33]. Therefore, further study is required to determine whether the monitoring of LH surge is required for patients undergoing pre-determined elective-freeze-all cycles. Addressing this issue, a recent retrospective study reported similar implantation and live birth rates for flexible PPOS (which uses freeze-all methodology) and flexible GnRH antagonist treatment [25]. No premature ovulation was detected, although LH levels were not monitored throughout the whole COH [25]. A retrospective study conducted by Zhu et al. revealed that ovarian stimulation in the late follicular phase can be performed without any exogenous pituitary inhibitors, reporting no cases of premature LH surge [34]. In the current study, LH increases ≥ 10 mIU/ml were observed in 3 and 10 patients in the PPOS and GnRH antagonist groups, respectively. Patients in the PPOS group and 4/5 patients in the GnRH group who underwent fresh embryo transfer produced live births. This illustrates the need for studies investigating the cut-off level for premature LH surge. The present results indicated that both endogenous increases in LH and low LH levels can affect reproductive outcomes. A recent retrospective cohort study of a GnRH antagonist protocol by Luo et al. [35] reported that low LH levels (< 4 IU/L) decreased the live birth rate in the fresh embryo transfer cycle, but not in the freeze-all cycle. They also noted that higher LH levels were associated with significantly lower CLBR than lower LH levels (63.1% vs. 68.3%, respectively, P = .517). This caused them to question whether serum LH levels during COS can be a useful biomarker during COS. Monitoring LH levels throughout COS may aid physicians in controlling the process.

The current study demonstrates that patients with normal ovarian reserve can still exhibit variations in the ovarian response. While rates of low and high ovarian response were low, live births occurred in both patients with low and high response in both groups. However, patients with low ovarian response had a lower CLBR than those with normal ovarian response. Accordingly, researchers have proposed the concept of an individualised COS protocol for managing patients with different ovarian responses [36]. For example, patients with low response should be administered appropriate medicine to improve ovarian sensibility, such as clomiphene citrate [37]. For high ovarian responders, the freeze-all strategy may be a good choice for reducing the risk of OHSS, although it may increase economic pressure due to the need to freeze surplus embryos. Further studies are required to determine whether frozen embryo transfer has an adverse effect on live birth [38], and whether mild ovarian stimulation combined with fresh embryo transfer is more appropriate for patients with infertility who exhibit high ovarian response.

The main strength of this study was the use of CLBR as the primary outcome to assess the ultimate effect of the first IVF cycle in patients with normal ovarian reserve, which is the most common population encountered in clinical settings. Physicians should consider all potential complicating factors, including cost of extra cryopreservation, safety regarding OHSS for high responders, and patient choice. Furthermore, our study simulated the real-world environment, in which fresh embryo transfer is performed first according to patient choice or conditions permitted by the GnRH antagonist protocol, followed by transfer of surplus embryos. When employing the PPOS protocol, all embryos should be frozen given that progestin results in a false synchronisation of the endometrium, and delayed frozen embryo transfer must be performed in the physiological state. However, an obvious advantage of the PPOS protocol over GnRH-ant is the use of an oral agent instead of daily injections. Despite these strengths, the study was limited by its single-centre design and small sample size. Larger and multi-centre prospective analyses should be conducted to assess CLBRs in participants of different ages and embryo stages. Moreover, the developmental potential of children born from this strategy should be monitored.

In this study, the risks and benefits of the two treatments were considered before the stimulation protocol was chosen. The GnRH-ant protocol is preferable for women with a good prognosis who would prefer shorter time to pregnancy. However, frequent monitoring is necessary, and the protocol has an unavoidable risk of late OHSS induced by pregnancy [31, 32]. PPOS is a new, simplified protocol for ovarian stimulation that is appropriate for the freeze-only strategy. PPOS has the advantages of fewer injections, lower cost, and being patient friendly. However, it has the disadvantages of delayed embryo transfer and an extended treatment time. Currently, PPOS is first considered only for patients who require all embryos to be frozen, such as patients with cancer and fertility preservation. For patients with a good prognosis, there are no relevant data on the cost-effectiveness of PPOS and the freeze-all approach in terms of medical or economic significance. Thus, it is critical to conduct RCTs that compare an elective freeze-only approach and PPOS to usual care in terms of clinical and cost effectiveness.

Conclusion

Our trial demonstrated that the GnRH antagonist and PPOS protocols produced the same number of embryos and similar pregnancy outcomes in young women with infertility. The ability of oral progestin to prevent premature ovulation was also similar to that of GnRH antagonists in women with normal ovarian reserve. These results support the efficacy and safety of PPOS. Thus, PPOS is likely to play a promising role in the freeze-only strategy given its simplicity and convenience for the patient.

Abbreviations

GnRH, gonadotropin-releasing hormone; PPOS, progestin-primed ovarian stimulation;

GnRH-ant, GnRH antagonist; IVF, in vitro fertilisation; CLBR, cumulative live birth rate; LH, luteinising hormone; COS, controlled ovarian stimulation; ICSI, intracytoplasmic sperm injection; COH, controlled ovarian hyperstimulation; OHSS, ovarian hyperstimulation syndrome; hCG, human chorionic

gonadotropin; PCOS, polycystic ovary syndrome; RCT, randomised controlled trial; IRB, Institutional Review Board; AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone; MPA, medroxyprogesterone acetate; IU, intrauterine; hMG, human menopausal gonadotropin; MC, menstrual cycle; SC, subcutaneous; IM, intramuscular; FET, frozen embryo transfer; OPU, oocyte pickup; HRT, hormone replacement treatment; SD, standard deviation; AFC, antral follicle count; GABA, gamma-aminobutyric acid

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shanghai East Hospital (Institutional Review Board number: 2018-17). All patients provided written informed consent to participate in this study.

Consent for publication

All patients provided their consent for data to be used for this research and publication.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Dr. Sun, Dr. Chen, and Dr. Ye were the chief investigators who completed the entire study, including procedures, conception, design, and completion. XX, SLY, and QY analysed the data and drafted the manuscript. WH, QXX, and TH were responsible for data collection. XSG was in charge of embryos. All authors approved the final manuscript.

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Tables

Table 1. Demographic and basic characteristics of the patients in two groups.

	PPOS with MPA (n=174)	GnRH antagonist (n=174)	P value
Age (years)	32.12 ± 3.69	32.11 ± 4.1	0.989
BMI (kg/m^2)	21.85 ± 3.2	21.75 ± 3.2	0.785
Duration of infertility (years)	3.88 ± 2.39	3.43 ± 2.54	0.095
Primary infertility, n (%)	123 (70.69)	114 (65.52)	0.301
AFC (n)	9.92 ± 3.89	9.98 ± 4.22	0.885
AMH (ng/ml)	3.41 ± 1.73	3.63 ± 2.48	0.560
Baseline hormonal profile			
bFSH (mIU/mL)	7.17 ± 1.6	7.31 ± 1.76	0.44
bLH (mIU/mL)	4.22 ± 2.17	4.23 ± 2.16	0.973
bE2 (pg/ml)	40.52 ± 12.14	39.99 ± 13.5	0.701
bP (ng/ml)	0.53 ± 0.48	0.53 ± 0.52	0.887
Cause of infertility, n (%)			
Tube factor	93 (53.45)	90 (51.72)	0.830
Male factor	41 (23.56)	38 (21.84)	0.798
Combined factors	35 (20.11)	40 (22.99)	0.602
Unexplained factor	5 (2.88)	6 (3.45)	0.759

Data are presented as mean ± SD or n (%); BMI, body mass index; AFC, antral follicle count; AMH, anti-Mullerian hormone; bFSH, basal follicle stimulating hormone; bLH, basal luteinizing hormone; bE2, basal estradiol; bP, basal progesterone; PPOS, progesterone-primed ovarian stimulation. MPA, Medroxyprogesterone acetate; GnRH, gonadotropin releasing hormone.

Table 2. Outcomes of stimulation and hormonal data in two groups.

Data are presented as mean ± SD or n (%).

SD, Standard deviation; hMG, human menopausal gonadotropin; MII, metaphase II; OPU, oocyte pick-up, PPOS, progesterone-primed ovarian stimulation.

Table 3. Pregnancy outcomes between the two groups.

	PPOS with MPA (n=174)	GnRH antagonist (n=174)	P-value
Duration of stimulation (days)	9.03 ± 1.56	8.64 ± 1.75	0.029
Total hMG dosage (IU)	1909.05 ± 421.77	1828.88 ± 503.77	0.108
LH value on trigger day (mIU/ml)	2.30 ± 1.78	3.66 ± 3.52	0
P-value on trigger day (ng/ml)	0.74 ± 0.41	0.99 ± 0.63	0
P-value on the day after trigger (ng/ml)	3.80 ± 1.91	4.17 ± 2.39	0.11
No. of oocytes retrieved (n)	9.88 ± 5.31	9.14 ± 5.12	0.185
Oocyte retrieved rate (%)	82.69 (1706/2063)	83.34 (1591/1909)	0.612
No. of MII stage oocytes (n)	8.13 ± 4.66	7.49 ± 4.23	0.182
No. of day-3 top-quality embryos (n)	4.04 ± 2.60	3.80 ± 2.25	0.385
No. of viable embryos (n)	4.60 ± 2.58	4.44 ± 2.03	0.518
Premature ovulation	0	0	NA
No. of incidence of LH surge (n)	0	6	NA
The proportion of viable embryos per oocytes (%)	46.95 (801/1706)	48.59 (773/1591)	0.348
Trigger-OPU time interval (h)	36.28 ± 0.66	35.71 ± 1.74	0.001

	PPOS with MPA (n=174)	fGnRH antagonist (n=174)	P value
FET cycles (n)	200	195	
Endometrial thickness on FET day (mm)	10.75 ± 2.05	10.42 ± 2.08	0.169
Transferred embryos %(n/T)			0.570
Single embryo transfer	13.50 (27/200	15.90 (31/195)	
Two embryos transfer	86.50 (173/200)	84.10 (164/195)	
Stages of embryos transferred % (n/total)			0.032
Cleavage embryo	90.88 (339/373)	94.99 (341/359)	
Blastocyst embryo	9.12 (34/373)	5.01 (18/359)	
Pregnancy outcome			
Implantation rate (%)	37.27 (139/373)	36.77 (132/359)	0.939
Biochemical pregnancy rate (%)	64 (128/200)	63.59 (124/195)	0.932
Clinical pregnancy rate (%)	57 (114/200)	55.89 (109/195)	0.825
Miscarriage rate (%)	12.28 (14/114)	13.76 (15/109)	0.742
Ectopic pregnancy rate (%)	1.75 (2/114)	0.92 (1/109)	1
CLBR (%)	55.75 (97/174)	52.87 (92/174)	0.591
Twin pregnancy rate (%)	22.81 (26/114)	22.94 (25/109)	0.982
Gestation (weeks)	38.25 ± 1.45	38.52 ± 1.68	0.762
Newborn birthweight (g)			
Single	3330.27 ± 487.52	3347.64 ± 393.53	0.837
Twin	2404.63 ± 548.15	2464 ± 331.02	0.527

Data are presented as mean ± SD or n (%).

FET, frozen embryo transfer; T, total; CLBR, cumulative live birth rate.

Table 4. Pregnancy outcomes between the fresh embryo transfer and freeze embryo transfer in the GnRH-ant protocol.

	FET (n=115)	ET (n=80)	P value
Transferred embryo %(n)			0.001
Single embryo transfer	8.70 (10/115)	26.25 (21/80)	
Two embryos transfer	91.30 (105/115)	73.75 (59/80)	
Stages of embryo transferred %(n)			0.001
Cleavage embryo	91.82 (202/220)	100 (139/139)	
Blastocyst embryo	8.18 (18/220)	0	
Pregnancy outcome			
Implntation rate %(n/T)	35 (77/220)	39.57 (55/139)	0.382
Biochemical pregnancy rate %(n/T)	64.34 (74/115)	62.5 (50/80)	0.792
Clinical pregnancy rate %(n/T)	53.91 (62/115)	58.75 (47/80)	0.503
Miscarriage rate %(n/T)	16.13 (10/62)	10.64 (5/47)	0.41
Twin pregnancy rate %(n/T)	25.81 (16/62)	19.15 (9/47)	0.413
Newborn birthweight (g)			
Single	3277.58 ± 424.30	3390.59 ± 367.49	0.248
Twin	2468.75 ± 376.69	2455.56 ± 238.68	0.894

Data are presented as mean ± SD or n (%).

ET, embryo transfer.

Table 5. CLBR in patients with low and high ovarian response.

	PPOS group	GnRH-ant group
Low ovarian response%(n/Total)	36% (9/25)	30% (9/30)
High ovarian response%(n/Total)	58.62% (17/29)	52.94% (9/17)

Figures

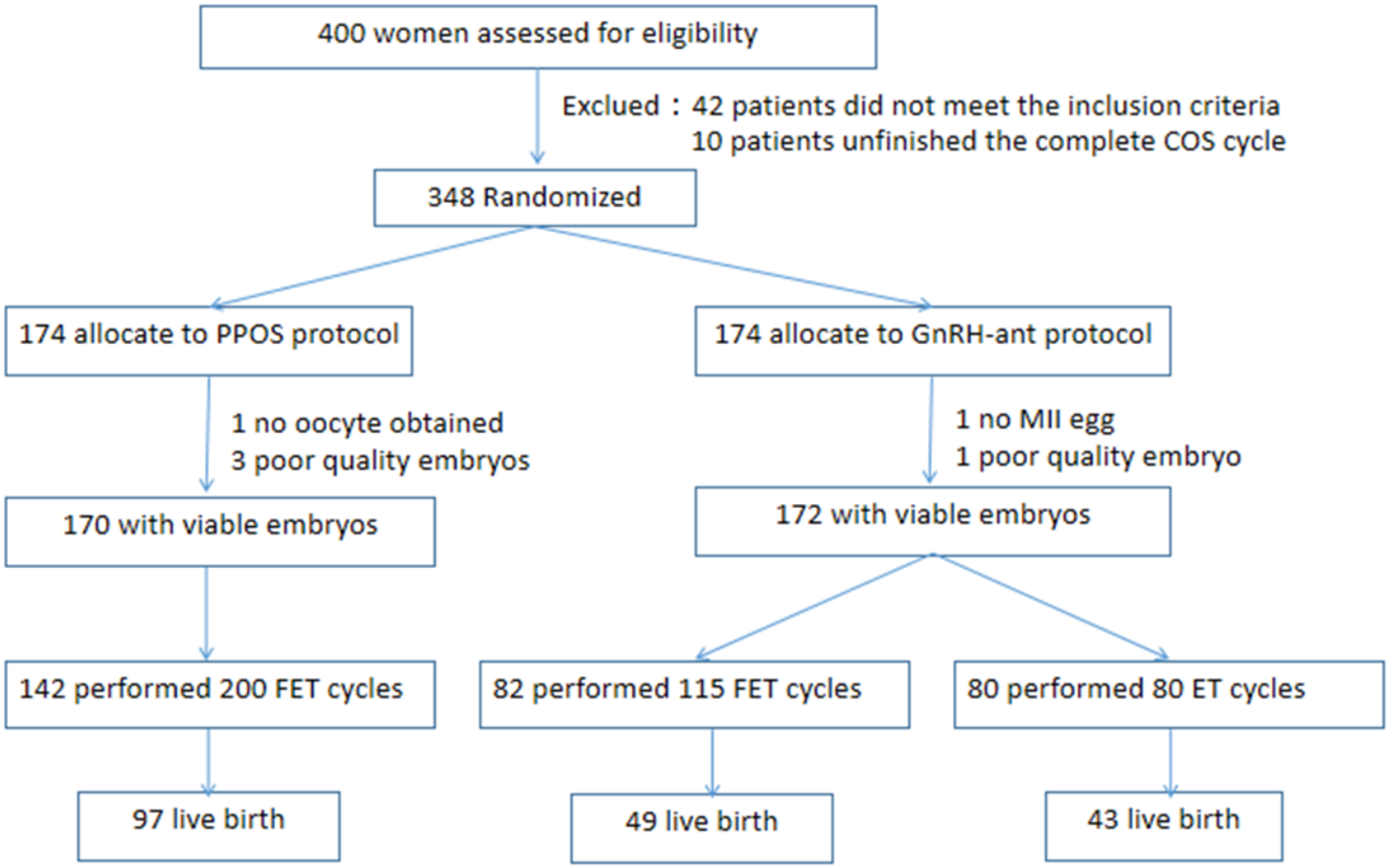

Figure 1

Flowchart of the study.

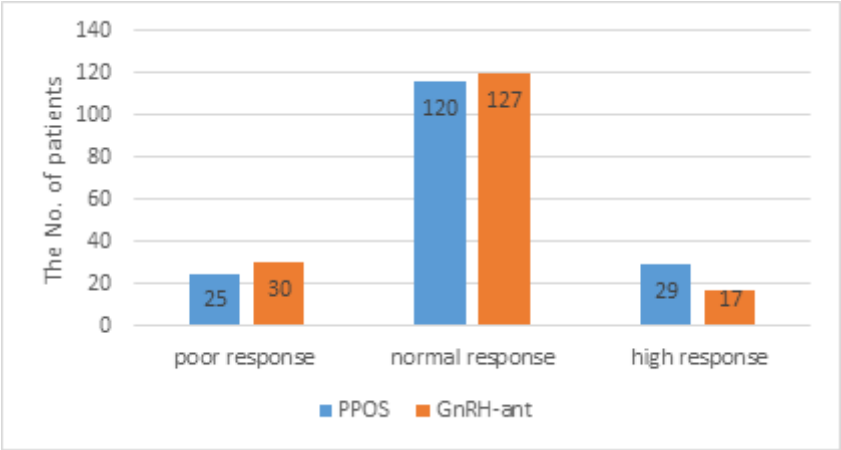

Figure 2

Different ovarian response in the two groups.