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Comparison of a progestin-primed ovarian stimulation protocol with a flexible GnRH antagonist protocol in patients with polycystic ovary syndrome who are participating in an IVF programme: study protocol for a randomised controlled trial

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ABSTRACT

Introduction Women with polycystic ovary syndrome (PCOS) undergoing in vitro fertilization (IVF) protocols are typically characterised by an increased number of oocytes retrieved. The oocytes are often of poor quality, leading to lower pregnancy rates, higher miscarriage rates and an increased risk of developing ovarian hyperstimulation syndrome (OHSS). Since our previous preliminary study showed that a novel progestin-primed ovarian stimulation (PPOS) protocol blocked the luteinising hormone (LH) surge during IVF and achieved a higher pregnancy rate with a lower incidence of OHSS, we designed a prospective randomised controlled trial to compare the efficacy and safety of this PPOS protocol with the flexible gonadotropin-releasing hormone (GnRH) antagonist protocol in patients with PCOS who are undergoing IVF procedures.

Methods and analysis Patients with PCOS will be randomised to one of two controlled ovarian stimulation regimens—GnRH antagonist or PPOS—using a computer-generated random number. A freeze-all strategy using embryo vitrification techniques and frozen embryo transfer will be performed in both groups. The primary outcome is the live-birth rate per transfer. Secondary outcomes include the incidence of premature LH surges, the duration and total dose of human menopausal gonadotropin stimulation, the number of oocytes retrieved, the incidence of moderate or severe OHSS, the number of embryos available for transfer, implantation rates, clinical pregnancy rates, pregnancy loss rates, ectopic pregnancy rates, pregnancy and neonatal complications, and congenital anomalies. The necessary sample size for this trial was estimated as 392 participants, with 196 participants in each group. Intention-to-treat analysis was used in processing our experimental data.

Ethics and dissemination This study was approved by the Institutional Review Board of the hospital (2016-133-T82). The trial will be conducted according to the principles of the World Medical Association's Declaration of Helsinki and in accordance with Good Clinical Practice standards. The findings of this trial will be published in a peer-reviewed journal.

Trial registration number ChiCTRIPR16009580.

Strengths and limitations of this study

- This is the first randomised controlled trial to examine the efficacy and safety of a novel progestin-primed ovarian stimulation protocol in patients with polycystic ovary syndrome (PCOS) who are undergoing IVF treatment.
- This study was performed in a single centre, and embryos were graded by the same trained embryologists, thereby avoiding the use of different embryo quality criteria from multiple centres.
- The individual eligibility criteria used in our study also limit the bias of advanced age, which is associated with a higher risk of adverse outcomes.
- A limitation is that this trial protocol only targets infertile patients with PCOS.
- This clinical trial is limited in that not all patients will be routinely assessed for ovarian hyperstimulation syndrome (OHSS), and thus, the reported incidence of OHSS is not accurate.

INTRODUCTION

Polycystic ovary syndrome (PCOS)—a common metabolic dysfunction and heterogeneous endocrine disorder—is the most common cause of anovulatory infertility, affecting approximately 10%–18% of reproductive age women worldwide.[1 2] It is usually characterised by a clustering of hyperandrogenism, hypersecretion of luteinising hormone (LH) and hyperinsulinaemia, which could result in the arrest of ovarian

follicular growth, oligo-ovulation or anovulation, menstrual dysfunction, hirsutism, infertility, pregnancy and/or neonatal complications.[3 4]

Women with PCOS undergoing IVF treatment because of infertility are increasing in number, and these patients have been well described, typically characterised by producing an increased number of oocytes; however, the oocytes retrieved from PCOS women are often of poor quality—leading to lower fertilisation, implantation, and pregnancy rates and a higher miscarriage rate and incidence of ovarian hyperstimulation syndrome (OHSS).[5–7] Increasing evidence raises the issue that impaired oocyte maturation and developmental competence in women with PCOS are possibly linked to abnormal endocrine/paracrine factors, metabolic dysfunction and alterations in the intrafollicular microenvironment during folliculogenesis and follicle maturation.[8–10] Thus, it will be of crucial importance to optimise clinical stimulation protocols to improve oocyte maturation and embryonic developmental competence in order to enhance pregnancy outcomes in women with PCOS undergoing IVF treatment.

Several clinical ovarian stimulation protocols have been used thus far in women with PCOS undergoing IVF treatment to prevent a premature LH surge during controlled ovarian stimulation (COS); these primarily include gonadotropin-releasing hormone (GnRH) agonist or antagonist protocols.[11 12] GnRH antagonists can competitively inhibit endogenous GnRH and produce an immediate and rapid decline in LH and follicle-stimulating hormone (FSH) levels without the flare effect of a GnRH agonist, and their administration by subcutaneous injection in the late follicular phase prevents an LH surge.[13 14] Previous randomised controlled trials of women with PCOS in which a GnRH antagonist protocol was compared with a conventional GnRH agonist protocol have reported similar clinical pregnancy rates for the two groups; however, IVF cycles with GnRH antagonists had lower gonadotropin requirements, a shorter duration of stimulation and a lower incidence of OHSS.[15]

With progress in embryo vitrification techniques, many studies have suggested that pregnancies that arise from the transfer of frozen-thawed IVF embryos appear to have better perinatal and pregnancy outcomes.[16 17] Similarly, a recent study conducted in China also reported that frozen embryo transfer (FET) resulted in a higher frequency of live births and a lower frequency of pregnancy loss and OHSS compared with fresh embryo transfer among infertile patients with PCOS.[18] Thus, GnRH antagonist regimens combined with a freeze-all strategy for women with PCOS are currently accepted as the most routine IVF procedures.

We first used progestins to prevent a premature LH surge during COS in a patient population with PCOS—that is, progestin-primed ovarian stimulation (PPOS)—and the prospective pilot trial showed that the progestin administered orally persistently suppressed LH concentrations in the serum without an LH surge during ovarian stimulation. Subsequently, with the freeze-all strategy, the FET cycles thus achieved higher ongoing pregnancy (58.67%) and live-birth rates (54.67%) relative to the previously reported live-birth rate of approximately 40% with GnRH antagonists in PCOS women undergoing IVF treatment.[19 20] These data indicated that progestin treatment might improve oocyte quality compared with a GnRH antagonist during COS in these patients, plus there were the advantages of an oral administration route instead of repeated injections of GnRH antagonist, a lower drug price and more control over LH levels, which can reduce the patients' discomfort and costs. However, there are currently no data comparing the efficacy and safety of the PPOS and GnRH antagonist protocols in improving the oocyte quality for PCOS patients. Therefore, we hypothesised that progestin would show some superiority in effectively improving oocyte maturation and developmental competence compared with using a GnRH antagonist. Thus, we have developed the present well-designed, large-sample prospective trial to investigate the potential of using progestin in women with PCOS who are undergoing IVF treatment.

METHODS AND ANALYSIS

Objectives

The purpose of this trial is to compare the efficacy and safety of the PPOS protocol to the flexible GnRH antagonist protocol in patients with PCOS who are undergoing IVF procedures.

Design of the trial

In this prospective, non-inferiority trial, we will compare the efficacy and safety of the GnRH antagonist and PPOS protocols in 392 patients with PCOS undergoing IVF. Participants with PCOS need to undergo IVF treatment because of infertility and will continue to be enrolled in the Shanghai Ninth People's Hospital affiliated with Shanghai Jiaotong University School of Medicine. This study has been approved by the Institutional Review Board (IRB) of Shanghai Ninth People's Hospital (2016-133-T82). Before the trial, investigators are required to provide all information related to the clinical trial, including the possible benefits and risks, other therapeutic choices and the right to withdraw, via a written consent form approved by the IRB. After being provided with sufficient time to decide whether to participate and the opportunity to ask questions, all participants will be required to provide written informed consent before study inclusion.

This protocol has been written in accordance with the Standard Protocol Items of the Recommendations for Interventional Trials (SPIRIT). A SPIRIT checklist is provided in online supplemental file 1. Any significant modification to the protocol requires a formal protocol amendment with unanimous agreement by the project team and approval by our IRB. Minor administrative

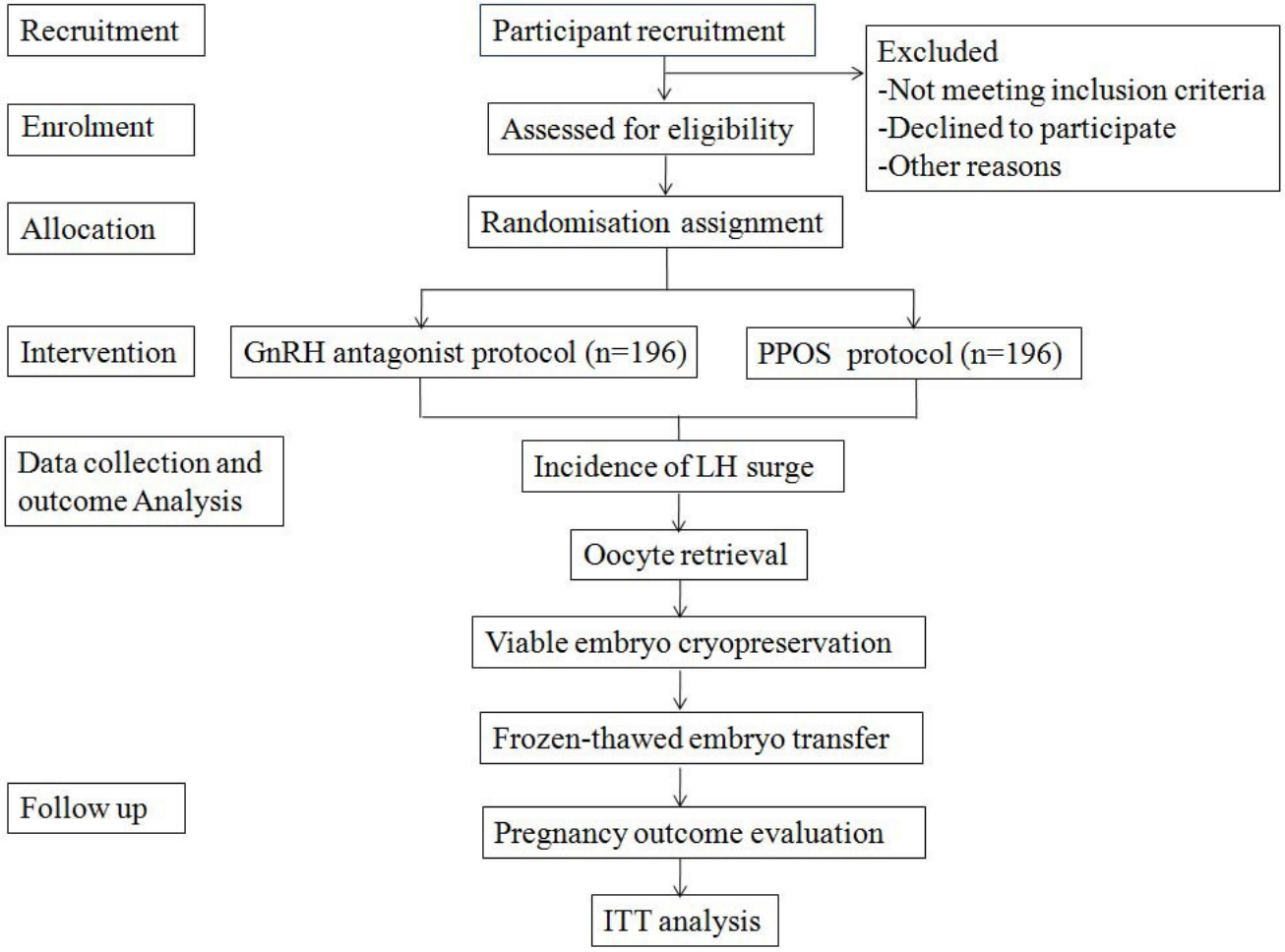

Figure 1 Flowchart of our randomised controlled trial comparing PPOS with a GnRH antagonist in patients with PCOS. GnRH, gonadotropin-releasing hormone; ITT, intention to treat; LH, luteinising hormone; PPOS, progestin-primed ovarian stimulation.

changes to the protocol will be documented in a memorandum. The study flowchart is shown in figure 1.

Eligibility criteria

Eligible patients need to meet all of the following inclusion criteria and there are no listed exclusion criteria.

Inclusion criteria

The following are our inclusion criteria:

1. Women who have a history of infertility ≥1 year.
2. Women aged between 20 and 35 years.
3. Women diagnosed with PCOS according to the modified Rotterdam criteria: oligomenorrhea or amenorrhea, together with the presence of ≥12 antral follicles (≤9 mm) and/or ovarian volume >10 mL on transvaginal ultrasonographic scanning, and/or clinical/biochemical hyperandrogenism.[21] Other causes of hyperandrogenism and ovulation dysfunction—including tumours, congenital adrenal hyperplasia, hyperprolactinaemia and thyroid dysfunction—were excluded.

Exclusion criteria

Women who met any of the following criteria were excluded:

1. Endometriosis grade 3 or higher.
2. Documented ovarian failure, including basal FSH above 10 IU/L.
3. Clinically significant systemic disease, or other endocrine disorders, including 21-hydroxylase deficiency, uncorrected thyroid disease or suspected Cushing's syndrome.
4. Patients who in the previous 3 months received hormonal treatments or other medications known to affect reproductive function, including oral contraceptives and GnRH agonists.
5. Patients were also excluded from the study if they had a history of unilateral oophorectomy, recurrent spontaneous abortion (defined as three or more previous spontaneous pregnancy losses), congenital or acquired uterine malformations, abnormal results on parental karyotyping or medical conditions that contraindicated assisted reproductive technology or pregnancy.
6. Inability to comply with the study procedures.

Recruitment of study participants

The trial protocol (12 January 2017, version 2.0) was approved by the IRB of Shanghai Ninth People's Hospital. Recruitment into the trial started in March 2017 and will continue until 392 participants are registered. All

participants who meet the abovementioned criteria will receive oral and written participant information from their attending physician before giving written informed consent. This study is being conducted at the Department of Assisted Reproduction of Shanghai Ninth People's Hospital (Shanghai, China).

Randomisation

Volunteers who met the abovementioned criteria will be allocated randomly to one of the two study groups in a ratio of 1:1 on menstrual cycle day 3. The allocation sequence will be generated with computer-generated random numbers. Both study investigators and participants will be aware of the allocation after ovarian stimulation. The doctors, embryologists and research coordinators involved in oocyte retrieval and embryo transfer will be blinded to the intervention group assignments in the trial.

Treatment method

Ovarian stimulation protocols

PPOS protocol

The PPOS protocol is as previously reported: human menopausal gonadotropin (hMG) (Anhui Fengyuan Pharmaceutical, China) at a dose of 150 to 225 IU/day and 10 mg of medroxyprogesterone acetate (MPA) (Beijing Zhong Xin Pharmaceutical, China) are administered daily from day 3 of menstruation until the trigger day.[19] The starting dose of hMG is 150 IU/day for patients with a high antral follicle count >20 or slightly elevated basal FSH (7–10 IU/L), and a daily dose of 225 IU hMG is used for the other patients. The dose was adjusted after day 5 of stimulation based on the ovarian response as assessed by serum hormone levels and transvaginal ultrasonography. As soon as three dominant follicles reached 18 mm in diameter, the final stage of oocyte maturation was co-triggered by triptorelin (100 µg) (Ferring International Center SA, Germany) and 1000 IU of human chorionic gonadotropin (hCG) (Lizhu Pharmaceutical Trading, China).

GnRH antagonist protocol

In the flexible GnRH antagonist protocol (antagonist group), we initiated daily s.c. administration of ganirelix (0.25 mg, Orgalutran, Organon, The Netherlands) when at least one of the following criteria was fulfilled: (1) the presence of at least one follicle measuring 12 mm; (2) serum E_2 levels of 600 pg/mL or (3) serum LH levels of 10 IU/L.[22] hMG (150–225 IU) is administered daily from menstrual cycle day 3, and follicular monitoring is performed every 2 to 3 days after 5 days of injections. The dose of hMG is adjusted according to the ovarian response, as monitored by ultrasonography and the measurement of serum sex steroids. Treatment with hMG and GnRH antagonist continue daily until the day when final oocyte maturation is triggered. When the dominant follicles reach a diameter of 18 mm, the final stage of oocyte maturation is induced with injections of 100 µg of triptorelin s.c combined with 1000 IU of hCG i.m. Transvaginal ultrasound-guided oocyte retrieval was performed 36 hours later.

Embryo culture, evaluation and cryopreservation

All of the follicles greater than 10 mm in diameter are aspirated. The oocytes are inseminated approximately 4–6 hours after follicular aspiration by a conventional IVF method or intracytoplasmic sperm injection, based on the sperm quality. Morphological criteria are then used for embryo scoring. On day 3, high-quality embryos are cryopreserved by means of vitrification in both groups undergoing FET. While the non-top-quality embryos are cultured for an extended period, only blastocysts with good morphology are frozen on days 5 or 6 according to Cummins' criteria.[23]

Endometrial preparation and frozen-thawed embryo transfer

It was previously reported that letrozole use is relevant and, if necessary, can be combined with a low dose of hMG to mildly stimulate follicular growth for endometrial preparation in frozen-thawed embryo transfer cycles.[19] We therefore administered 5 mg of letrozole from cycle days 3 to 7 and then monitored follicle growth beginning on day 10. At times, the treatment includes a low dose of hMG (75 IU/day) to stimulate the growth of follicles and the endometrial lining. Finally, we administered 5000 IU of hCG to trigger ovulation, and the timing of FET was performed as described elsewhere.[24] For patients with a thin endometrium or failed embryo transfer after mild stimulation cycles, we adopt hormonal replacement therapy as described elsewhere.[19 24] The maximal number of transferred embryos is two per transfer cycle. When pregnancy is achieved, progesterone supplementation is continued until 10 weeks of gestation.

Outcome measurements

Primary endpoints

The primary outcome is the live-birth rate per randomised cycle. A live birth is defined as the delivery of any viable infant at 28 weeks or longer gestation after embryo transfer.

Secondary endpoints

Secondary outcome measures are the incidence of premature LH surges, duration of hMG stimulation, total dose of hMG, E_2 and progesterone concentrations on the trigger day, cycle cancellation rate, number of cumulus-oocyte complexes () retrieved, number of metaphase II oocytes, fertilisation rates, number of viable embryos for transfer, biochemical pregnancy and clinical pregnancy rates, implantation rates, ongoing pregnancy and live-birth rates per transfer, and cumulative live-birth rates (including all frozen embryo transfers from a single IVF cycle).

A premature LH surge is defined as an increase in serum LH levels more than twice the baseline level or a serum LH >15 mIU/mL and increased serum progesterone level >2.5 ng/mL on the trigger day.[24] Biochemical

pregnancy was defined as a hCG concentration of more than 10 mIU/mL, as measured 14 days after embryo transfer. An ongoing pregnancy and clinical pregnancy were defined as the presence of a gestational sac with fetal heartbeat detection at 12 weeks and at 6–7 weeks of gestation, respectively. All of the pregnancy and neonatal outcomes were obtained through a review of medical records.

Safety endpoints

The safety endpoints include the incidence of moderate or severe OHSS, miscarriage rates, ectopic pregnancy, pregnancy complications, congenital anomalies and neonatal complications.

The definition and classification of OHSS are adopted according to the accepted criteria previously reported.[25 26] Mild OHSS is diagnosed by the presence of abdominal distension and/or discomfort with or without nausea, vomiting, abdominal pain, dyspnoea, diarrhoea, enlarged ovaries and no important alterations in laboratory features. Moderate OHSS is diagnosed by ultrasonographic evidence of ascites (in addition to the above mild clinical features), with haemoconcentration (Hct >41%) and elevated white cell count (>15×10^9/L). Severe OHSS is diagnosed by the presence of clinical evidence of ascites and/or hydrothorax, severe dyspnoea, oliguria/anuria, intractable nausea/vomiting, severe haemoconcentration (Hct >55%), white cell count >25×10^9/L, creatinine clearance (CrCl) <50 mL/min, creatinine (Cr) >1.6 mg/dL, sodium (Na+)<135 mEq/L, potassium (K+)>5 mEq/L, elevated liver enzymes and so on.[27]

Data management, monitoring, safety and auditing

The time points for enrolment, intervention and data collection are described in figure 2. Study-related information—such as participant identity and data and medical records related to the study— will remain confidential.

Data collected will be entered and stored in password-protected electric case report forms (eCRFs) with access only allowed to the researchers involved. As with previous reports, we will use an automated system for validating the data against a set of predefined rules that query investigator data entered as invalid, illogical or incomplete. Data elements critical to the trial are double-checked to confirm the accuracy of the data entered compared with the source documents.[24]

The data monitoring committee comprises three clinical trial specialists, including a biostatistician, who were not associated with this study. The committee will meet at least two times a year, and all of the data obtained from the current trial will be checked by the committee. Monitors will ensure that the investigational team is complying with the study protocol and Good Clinical Practice (GCP) standards that the data and adverse events (AEs) are accurately and appropriately recorded in the eCRFs, that severe AEs (SAEs) are reported to the trial coordinator and the investigational drug provider and that those meeting the SAE reporting criteria are reported to the IRB. All participants with AEs will be followed up during the course of the AE until their resolution or for 4 weeks after the end of the trial. All SAEs will be reported to all investigators, discussed through a web-based AE reporting system and will be reported to the Pharmaceuticals and Medical Devices Agency, if necessary.

Sample size and power calculations

Previous studies have reported that the anticipated live-birth rate in the GnRH antagonist protocol followed by FET was over 40.0%, and our recent double-blind randomised crossover clinical trial of women with PCOS showed that with the PPOS protocol, the ongoing pregnancy rate per transfer was 58.67% (44/75) and the live-birth rate was 54.67% (41/75). Therefore, we hypothesised that the novel PPOS protocol would achieve a comparable live-birth rate for PCOS patients undergoing IVF treatment.

Therefore, with respect to power calculations, we designed this study to have a power of 80% at a two-sided significance level of 0.05 to detect an absolute difference of 10 percentage points in the live-birth rate between the two study groups (based on anticipated rates of 54.67% in the PPOS group versus 40% in the GnRH antagonist group, both after FET) by means of Pearson's χ^2 test. We calculated that at least 178 patients per study group were required, a number that we increased to 196 to allow for a dropout rate of 10%.

Statistical analysis

We will perform intention-to-treat analyses to compare the live-birth rates and the incidence of moderate and severe OHSS in the two study groups. Categorical data are represented as percentages and frequencies; differences in these measures between the two study groups will be assessed by means of Chi-square analysis, with the use of Fisher's exact-probability test used for expected frequencies of less than 5. Continuous data are expressed as the means (±SD), with Student's t-tests or a Kruskal-Wallis test for between-group differences. A multivariate logistic regression will be used to adjust for the effects of baseline characteristics. $p<0.05$ was considered a significant difference. All of the analyses were performed with SPSS software V.17.0.

Patient and public involvement

Patients and the public are not involved in the process of the study. The participants will be informed of the study results via peer-reviewed journals, conference presentations and the Clinical Research Information Service.

Ethics and dissemination

This study was approved by the IRB of Shanghai Ninth People's Hospital (2016-133-T82). The trial will be conducted according to the principles of the World Medical Association's Declaration of Helsinki and in accordance with GCP standards. The trial findings will be published in peer-reviewed journals. All confidential

Fig. 2

Time-point	Study period						
	Enrolment	Allocation	Post-allocation				
	Screening	Menstrual cycle day 3	Ovarian stimulation cycle monitor	Oocyte retrieval	Viable embryo cryopreservation	Frozen-thawed embryo transfer	Follow- up
Enrolment							
Identification	×						
Eligibility screen	×						
Baseline measures	×						
Informed consent	×						
Randomisation allocation		×					
Interventions							
GnRH antagonist protocol			←	—	—	→	
PPOS protocol			←	—	—	→	
Data collection and Assessments							
Demographic data	×						
Primary outcome measure							
Live-birth rates						×	
Incidence of OHSS			×				
Secondary outcome measure							
Incidence of LH surge			×				
Duration of hMG stimulation			×				
Total dose of hMG			×				
Cycle cancellation rate			×				
Oocyte retrieval				×			
Embryos available					×		
Pregnancy outcomes						×	×
Adverse events			←	—	—	→	
Complications			←	—	—	→	

Figure 2 Timetable of the study period.

patient data will be protected. The patients' identities will not be disclosed.

DISCUSSION

A high-quality oocyte is imperative for fertility, but PCOS patients consistently suffer from poor oocyte quality, resulting in decreased fertilisation rates, impaired pregnancy rates and higher miscarriage rates.[28 29] An increasing number of studies have shown that the production of oocytes with lower developmental competence from PCOS patients is related to abnormal endocrine/paracrine factors, metabolic dysfunction and alterations in the intrafollicular microenvironment during folliculogenesis and follicle maturation, including hypersecretion of LH, hyperandrogenism and hyperinsulinaemia.[8 30] Improving impaired oocyte developmental competence in women with PCOS to enhance pregnancy outcomes is therefore an urgent issue that requires resolution.

Women with PCOS typically demonstrate tonic hypersecretion of LH during the follicular phase, and high LH levels during folliculogenesis may directly activate premature meiotic processes and damage the oocyte nucleus, leading to apoptosis.[31 32] Hypersecretion of LH may also promote premature granulosa cell luteiniation and follicular atresia in small antral follicles, causing premature oocyte maturation via inhibition of oocyte maturation

inhibitors, all of which compromise the quality of both oocytes and embryos.[31] Elevated serum LH levels also contribute to hyperandrogenaemia by directly stimulating follicular theca cells to increase androgen biosynthesis.[33] It has been suggested that increased androgen concentrations in the follicular fluid may then exert a negative impact on oocyte developmental competence by decreasing oocyte calcium oscillations, consequently inhibiting oocyte cytoplasmic maturation and thus affecting meiotic maturation.[34]

Other studies have suggested that elevated testosterone—either directly or indirectly—decreases the rates of in vitro maturation (IVM), fertilisation and embryonic development.[35 36] All of the aforementioned studies suggested that elevated follicular LH and androgen levels exert a detrimental effect on oocyte/embryo quality and pregnancy outcomes in PCOS patients, although some studies showed that premature luteinisation did not affect the pregnancy rates.[37]

In our preliminary studies of PCOS women undergoing IVF treatment, progestin (MPA) administered orally persistently suppressed LH levels during ovarian stimulation, and we observed no cases of a premature LH surge. When this was followed by freeze-all and FET, a better ongoing pregnancy rate (58.67%) and live-birth rate (54.67%) were achieved.[19] The better pregnancy outcomes for PCOS patients using our novel PPOS protocol in IVF might be explained by the following: First, progestin administered orally from the early follicular phase can inhibit the synthesis and secretion of LH by reducing the frequency of the GnRH pulse, which may completely or partially correct abnormally high LH levels and hyperandrogenism in the intrafollicular milieu during folliculogenesis and follicle maturation in women with PCOS.[38 39] Second, some previous studies have shown that progesterone plays a crucial role in oocyte maturation, fertilisation and embryonic development, both directly and indirectly.[40] PCOS women manifest an accelerated conversion of progesterone to androstenedione in theca cells because of high LH stimulation, which leads to a paucity of progesterone in the intrafollicular microenvironment.[41 42] Therefore, there is a theoretical benefit from the addition of progestin during COS for patients with PCOS that would allow for normal follicle development in an appropriate microenvironment and improve oocyte quality, thus enhancing pregnancy outcomes.

Live-birth rates are the recommended end point for infertility trials.[43] The GnRH antagonist regimen followed by vitrified embryo transfer cycles combined with a freeze-all strategy for women with PCOS has recently become accepted as the most common routine IVF procedure. Acceptance is based on either the previous prospective or retrospective clinical study results.[13] We therefore selected the GnRH antagonist protocol as the control group to evaluate the efficacy and safety of our novel PPOS protocol in women with PCOS who are undergoing IVF treatment.

To our knowledge, this is the first randomised controlled trial to examine the efficacy and safety of PPOS ovarian stimulation protocols in IVF for women with PCOS compared with typical GnRH antagonist protocols. The present study results will add to the current knowledge base regarding COS and have the potential to establish a promising treatment option for PCOS patients.

Trial status

The present study was conceived and designed in 2016. The registry number is ChiCTRIPR16009580, and it was registered on 12 October 2016 (http://www.chictr.org.cn/showproj.aspx?proj=16352). The first participant was randomised on 20 March 2017. We will complete recruitment in March 2021, and our follow-up of pregnancies from FET will be ongoing. This protocol, version 2, was approved on 12 January 2017.

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Contributors NW participated in the design of the study. YW participated in the design and development, including the statistical analysis plan. QZ, MM, ZL and YT were responsible for collection of data. YK conceived of the study and guided the design. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient consent for publication Patients and the public are not involved in the process of the study. The participants will be informed of the study results via peer-reviewed journals, conference presentation and the Clinical Research Information Service.

Provenance and peer review Not commissioned; externally peer reviewed.

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