Using Letrozole Cotreatment With Progestin-Primed Ovarian Stimulation In Women With Polycystic Ovary Syndrome Treated For IVF

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Abstract

Background: Women with polycystic ovary syndrome (PCOS) often experience poor oocyte quality and a high risk of ovarian hyperstimulation syndrome (OHSS) when treated with controlled ovarian stimulation (COS) in vitro fertilization (IVF). Progestin-primed ovarian stimulation (PPOS) shows good potential to compete with conventional protocols in women with PCOS. However, it always accompanied by increased pituitary suppression and gonadotropin consumption. Letrozole (LE) has the ability to increase luteinizing hormone (LH) levels and appears to have the potential to alleviate pituitary inhibition during COS in women with PCOS. A retrospective cohort trial was performed to evaluate the efficacy of PPOS with or without letrozole in infertile women with PCOS.

Methods: This retrospective cohort study included 448 women with PCOS who underwent COS with human menopausal gonadotropin (hMG) and medroxyprogesterone acetate (MPA) (n=224) or hMG and MPA cotreatment with LE (n=224) from January 2018 to March 2021. Baseline characteristics of the two groups were balanced with propensity score matching using the nearest neighbour random matching algorithm at a ratio of 1:1. The primary outcome measure was the implantation rate. The secondary outcomes were the endocrinological profiles, gonadotropin dose and duration, number of oocytes retrieved and viable embryos, clinical pregnancy rate, miscarriage rate and ectopic pregnancy rates.

Result(s): The implantation rate was significantly higher in the study group than that in the control group (42.22% vs. 34.69%, $P < 0.05$). Compared with the control group, the study group had a higher LH concentration on the trigger day (3.85 ± 3.6 mIU/ml vs. 2.44 ± 1.71 mIU/ml, $P < 0.01$), but there was no case of premature LH surge or OHSS in both groups. The consumption of gonadotropin, the number of oocytes retrieved and viable embryos were similar between the two groups. Additionally, no difference was found in the clinical pregnancy rate, miscarriage rate or ectopic pregnancy rate.

Conclusion(s): This study shows that LE administration in the PPOS protocol was feasible to improve the implantation rate and alleviate profound pituitary suppression from progestin administration without interfering with its premature LH surge blockade effect but with a non-significant reduction in gonadotropin consumption in women with PCOS undergoing IVF treatment.

Introduction

Polycystic ovary syndrome (PCOS) is considered to be a highly prevalent endocrine and reproductive disorder and affects 5%-10% of women of reproductive age [1]. It is usually characterized by a heterogeneous syndrome of ovulatory dysfunction, polycystic ovarian morphology and hyperandrogenism [2, 3]. In vitro fertilization (IVF) serves as a third-line treatment for infertile PCOS patients who fail to respond to lifestyle modification or ovulation induction (OI) therapies [4]. However, women with PCOS treated with IVF often experience a high risk of OHSS because of excessive numbers of oocytes retrieved [5] and poor oocyte quality, leading to repeated transplantation failure [6]. Therefore, safer and more efficacious controlled ovarian hyperstimulation (COH) regimens need to be explored.

Progestin-primed ovarian stimulation (PPOS), a regimen that uses progestin as an alternative to the gonadotropin-releasing hormone (GnRH) analogue in the follicular phase to suppress the premature luteinizing hormone (LH) surge [7], has been approved to be an efficacy and safety in the population of women with PCOS [8] [9]. Nevertheless, the use of progestin in the PPOS regimen tends to inhibit the pituitary in a more profound manner and thus, higher doses of human menopausal gonadotropin (hMG) are required than those in the GnRH agonist short protocol for patients with or without PCOS[7] [8]. Thus, optimizing the PPOS protocol is always the direction we have been trying to explore.

Clomiphene citrate (CC) which was used to increase follicle-stimulating hormone (FSH) and LH secretion from the pituitary by blocking a negative estradiol feedback loop by binding to estradiol receptors in the hypothalamus, was adopted for cotreatment with PPOS in our previous study, and the results showed that CC could increase LH values and diminish hMG consumption but with a harvest of fewer oocytes[10, 11] and fewer top-quality embryos among women with PCOS [11]. Currently, letrozole appears to be a good alternative option in women with ovarian stimulation of PCOS, especially for those with CC resistance, due to its higher ovulation rate, pregnancy rate and live birth rate among patients with PCOS[12-14]. Different from the mechanism by which CC acts on hypothalamic estrogen receptors, LE decreases estradiol production and normal central negative feedback mechanisms remain intact [12]. Therefore, the clinical efficacy of letrozole combined with PPOS is worth exploring.

The present retrospective cohort trial was designed to investigate the effects of letrozole combined with PPOS protocol on the characteristics of the oocyte pick-up cycle and frozen embryo transfer (FET) cycle in PCOS female patients.

Materials And Methods

Study Setting And Patients

Women with PCOS who underwent IVF/ICSI cycles using PPOS (hMG + MPA) or PPOS cotreatment with letrozole (hMG + MPA + LE) from January 2018 to March 2021 were screened. This study was approved by the Ethics Committee (Institutional Review Board) of Shanghai Ninth People's Hospital. Patients met the following criteria: 1. Between 20 and 40 years of age; 2. Basal follicle-stimulating hormone FSH level <10 mIU/ml; and 3. no more than 1 no viable embryo cycle previously. The diagnosis of PCOS was made according to the 2003 Rotterdam consensus, in which at least 2 out of 3 of the following criteria were met [15]: 1) oligo- and/or anovulation; 2) biochemical and/or clinical evidence of hyperandrogenism; or 3) polycystic ovarian morphology on ultrasound. The following diseases were excluded: other aetiologies of hyperandrogenism and ovulatory dysfunction, including congenital adrenal hyperplasia, androgen-secreting tumours, hyperprolactinemia and thyroid disease. A flowchart of the study is shown in Figure 1.

Controlled Ovarian Stimulation

From menstrual cycle day 3 (MC3) to the trigger day, patients were coadministered 150-225 IU/d hMG (Anhui Fengyuan Pharmaceutical Co., China) via intramuscular injection and 4 mg/d MPA (Shanghai Xinyi Pharmaceutical Co., China) through oral administration. Letrozole (Jiangsu Hengrui Medicine Co., China) 2.5 mg/day was given from cycle day 3 onwards only for 5 days in the study group. The starting dose of hMG was 150 IU/day for patients with a high antral follicle count (>20) or slightly elevated basal FSH (7–10 mIU/ml), and a daily dose of 225 IU hMG was used for the other patients. For both groups, the hMG doses were adjusted depending on the number and size of the developing follicles on ultrasound as well as serum concentrations of sexual hormones, including FSH, LH, oestrogen (E₂) and progesterone (P), started on MC8 and every 2 to 4 days thereafter. The final stage of oocyte maturation was triggered by the combination of 0.1 mg triptorelin (Decapeptyl; Ferring Pharmaceuticals, Germany) and 1000 IU hCG (Lizhu Pharmaceutical Trading Co., China) once the leading follicle exceeded 20 mm or at least three follicles exceeded 18 mm in diameter. Oocyte retrieval was performed 34–36 hrs after the trigger and guided by transvaginal ultrasound (TVS). All follicles with a diameter over 10 mm were aspirated [16].

After oocyte retrieval, fertilization was carried out in vitro by either standard IVF or intracytoplasmic sperm injection (ICSI) according to semen quality and previous fertilization conditions [17-19]. Embryos were examined for the number or regularity of blastomeres and the degree of fragmentation. Top-quality embryos (including grade-1 and grade-2 6-cell embryos and above) were frozen by means of vitrification within three days after oocyte retrieval according to the criteria described by Cummins et al. [7, 20]. The non-top-quality embryos were placed in extended culture, and blastocysts with good morphology were also frozen on day 5 or 6 [7, 16, 21, 22].

Hormone Measurement

Serum FSH, LH, E₂ and P levels were measured on MC3, MC8, MC10-12, the trigger day and the day after trigger. Hormone concentrations were measured by means of chemiluminescence (Abbott Biologicals B.V., the Netherlands). The lower limits of sensitivity were as follows: FSH, 0.06 mIU/ml; LH, 0.09 mIU/ml; E₂, 10 pg/ml; and P 0.1 ng/ml. The upper limit for the E₂ measurement was 5000 pg/ml. If the E₂ level on the trigger day or the day after trigger was greater than the upper limit, it was recorded as 5000 pg/ml without repeating the assay after sample dilution.

Endometrial Preparation and Frozen Embryo Transfer

Endometrial preparation and FET were arranged for the second cycle after oocyte retrieval as previously described [7, 21]. Mild stimulation with letrozole was recommended for all patients, while hormone replacement therapy (HRT) was conducted for those who failed to become pregnant with mild stimulation cycles or with a history of a thin endometrium (endometrial thickness ≤6 mm). In the mild stimulation cycle, women were administered letrozole 2.5/5 mg for 5 days beginning at MC3. When the dominant follicle was ≥17 mm in diameter with an endometrial lining >8 mm, an E₂ level >150 pg/ml and a P level <1 ng/ml, a bolus of urinary hCG (5000 IU) was injected for ovulation triggering. Progesterone

commenced 2 and 3 days later, followed by day 3 embryo transfer 4 and 5 days later or blastocyst transfer 6 and 7 days later via abdominal ultrasound guidance.

Outcome Measures

The primary outcome measure of this study was the implantation rate in FET cycles. The secondary measures included the Gn dose and duration, the number of oocytes retrieved, the number of viable embryos, profound LH suppression (a serum LH level less than 1 mIU/ml on the trigger day during ovarian stimulation[23]) and incidence of premature LH surge (an increased serum LH level of 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 during ovarian stimulation [24]). As well as the clinical pregnancy rate, the miscarriage rate and ectopic pregnancy rate were recorded. The viable embryo rate per oocyte was defined as the number of viable embryos divided by the number of oocytes retrieved. The cycle cancellation rate was estimated based on the number of patients who had no viable embryos after complete oocyte retrieval. The implantation rate was calculated according to the number of gestational sacs divided by the number of embryos transferred. Clinical pregnancy was defined as the presence of at least one gestational sac with or without foetal heart activity by ultrasound examination at 4 weeks after FET divided by FET cycles. The miscarriage rate was based on the proportion of eventuated pregnancies in spontaneous or therapeutic abortion.

Statistical Analysis

A propensity score matching (PSM) model was established to balance differences in baseline characteristics between the two groups. To estimate the propensity score, we selected 10 covariates, namely, age, antral follicle count (AFC), basal levels of FSH, LH, E₂ and P, type of infertility (primary or secondary), infertility duration, previous IVF attempts (0, 1–2 or ≥3), and body mass index (BMI). Patients using MPA+hMG+LE were matched with the MPA+hMG group using the nearest-neighbour random matching algorithm at a ratio of 1:1. PSM was conducted using the R statistical programming language (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria).

The data were evaluated by Student's t-test for continuous variables with a normal distribution, the Mann-Whitney U-test for continuous variables with a nonnormal distribution, and presented as mean (standard deviation, SD). Pearson's chi-square test or Fisher exact test for categorical variables (presented as %), as appropriate. Data analysis was performed with the Statistical Package for the Social Sciences (version 24, SPSS Inc). Two - sided $P < 0.05$ was considered statistically significant.

Results

Patient Characteristics

Figure 1 shows a profile summary of the study. Briefly, a total of 2453 IVF/ICSI cycles were screened from our database, and 401 cycles were excluded as described in the Materials and Methods section. Of the remaining 2052 patients, 224 patients undergoing the MPA+ hMG +LE protocol were matched with 224 patients who used the MPA+ hMG protocol. All of these patients completed oocyte retrieval cycles and succeeded in producing oocytes (range, 1–62), while 34 patients had no viable embryos. Among the remaining patients, 371 women completed FET cycles. No significant between-group differences were found in the post-matching analysis with regard to any baseline characteristics (all $P>0.05$) (Table 1). The basic characteristics before matching are presented in Supplementary Table 1.

Table 1
Baseline characteristics of women undergoing IVF/ICSI.

Characteristic	Study group	Control group	P value
	(hMG+MPA+LE; n=224)	(hMG+MPA; n=224)	
Age (y), mean $\pm$ SD	31.79 $\pm$ 3.59	31.79 $\pm$ 3.51	0.99
BMI (kg/m ²), mean $\pm$ SD	24.15 $\pm$ 4.39	24.34 $\pm$ 4.02	0.64
Duration of infertility (y), mean $\pm$ SD	3.73 $\pm$ 2.46	3.42 $\pm$ 1.73	0.14
Primary infertility, n (%)	66.96 (150/224)	68.31 (153/224)	0.74
Indication, n (%)			0.92
Tubal factor	135	132	
Male factor	45	49	
Unknown factor	33	30	
Combination of factors	11	13	
Previous IVF failure, n (%)			0.34
0	195	194	
1–2	16	22	
> 3	13	8	
MC3 hormone levels, mean $\pm$ SD			
FSH (IU/L)	5.17 $\pm$ 1.22	5.17 $\pm$ 1.07	0.96
LH (IU/L)	5.07 $\pm$ 3.29	5.04 $\pm$ 3.24	0.91
E ₂ (pg/mL)	34.7 $\pm$ 11.54	33.72 $\pm$ 11.81	0.38
P (ng/mL)	0.25 $\pm$ 0.13	0.25 $\pm$ 0.11	0.91
AFC	20.52 $\pm$ 6.05	21.3 $\pm$ 7.03	0.21
Note: Data are presented as mean $\pm$ standard deviation or number (percentage).			

Table 2
Cycle characteristics of COS in the two groups.

Characteristic	Study group	Control group	P value
	(hMG+MPA+LE; n=224)	(hMG+MPA; n=224)	
hMG duration (d)	9.03±1.79	9.21±2.18	0.33
hMG dose (IU)	1949.89±725.03	2017.41±653.32	0.3
> 10-mm follicles on hCG day (n)	23.17±10	19.81±9.23	0
> 14-mm follicles on hCG day (n)	18.3±9.32	13.84±7.98	0
Percentage of women with profound pituitary suppression (%)	7.14(16/224)	14.29(32/224)	0.02
Punctured follicles (n)	24.43±0.86	23.8±0.88	0.61
Oocyte retrieved (n)	17.5±9.16	16.81±10.29	0.45
MII oocytes (n)	13.45±7.28	14.08±9.22	0.42
Fertilized oocytes (n)	11.66±6.47	12.54±8.39	0.21
Cleaved embryos (n)	10.43±5.78	11.29±7.5	0.17
High-quality embryos (n)	4.75±3.48	5.23±4.73	0.22
Blastocyst embryos (n)	1.73±2	1.53±2.33	0.33
All cryopreserved embryos (n)	5.48±3.25	5.37±4	0.75
Oocyte retrieval rate (%)	71.98(3921/5447)	71.27(3765/5283)	0.41
Mature oocyte rate (%)	76.74 (3009/3921)	83.77 (3154/3765)	0
Fertilization rate (%)	79.23 (2384/3009)	81.48 (2570/3154)	0.03
Cleavage rate (%)	97.86 (2333/2384)	98.40 (2529/2570)	0.16
Viable embryo per oocyte retrieved (%)	31.35 (1230/3924)	31.93 (1202/3765)	0.59
Cycle cancellation rate (%)	7.14 (16/224)	8 (18/224)	0.72
Note: Data are presented as mean ± standard deviation or number (percentage).			

Table 3
Pregnancy outcomes of frozen-thawed embryos from the two groups.

Outcome	Study group	Control group	P value
	(hMG+MPA+LE; n=224)	(hMG+MPA; n=224)	
Patients (n)	189	193	
FET cycles (n)	280	294	
Thawed embryos (n)	477	493	
Viable embryos after thawed (n)	477	493	
Endometrial preparation (n)			0.99
Natural cycle	47	49	
Mild stimulation	138	144	
Hormone therapy	95	101	
Endometrial thickness (mm)	10.4 ± 2.1	10.5 ± 2.1	0.89
Cumulate clinical pregnancy rate			0
Per embryo transfer (%)			0
Clinical pregnancy rate per transfer	54.29%(152/280)	49.32%(145/294)	0.23
Implantation rate (%)	42.14(201/477)	34.69%(171/493)	0.02
Miscarriage rate (%)	7.89 (12/152)	8.97%(13/145)	0.07
Ectopic pregnancy rate (%)	1.32(2/152)	2.07%(3/145)	0.68
Note: Data are presented as mean ± standard deviation or number (percentage).			

Ovarian Stimulation, Follicle Development, and Oocyte Performance

The MPA+ hMG and MPA+ hMG +LE groups had comparable numbers of oocytes retrieved (17.5 ± 9.16 vs. 16.8 ± 10.29 , $P > 0.05$) and viable embryos (5.48 ± 3.25 vs. 5.37 ± 4 , $P > 0.05$). However, the difference in mean hMG doses and durations of ovarian stimulation failed to reach statistical significance between the two groups ($P > 0.05$). The number of follicles with diameters larger than 10 and 14 mm on the trigger day was significantly higher in the study group ($P < 0.01$). There was a significantly lower mature oocyte rate (76.74% vs. 83.77%, $P < 0.01$) and fertilization rate (79.23% vs. 81.48%, $P < 0.05$) in the study group than these in the control group. The rates of cycle cancellation for nonviable embryos did not differ between the two groups. No premature LH surge or moderate-to-severe OHSS was observed during the study.

Hormone Profiles During Treatment

The endocrine dynamics of FSH, LH, E₂ and P during ovarian stimulation are presented in Figure 2. The FSH levels increased dramatically after hMG administration for 5 days and then remained stable until the trigger day. After the dual trigger, the FSH levels increased dramatically to nearly 20 mIU/ml. No significant differences were observed in FSH levels at any time point between the two groups.

During the whole process of COH, LH in the two groups always maintained a low level. However, there were differences in the change trend of LH between the two groups. LH in the control group showed a downward trend. However, in the study group, LH remained basically unchanged in the first five days, followed by a downward trend until the trigger day.. The LH values were significantly higher in the study group than those in the control group at each observation point during the COH ($P < 0.01$). In addition, there were significantly fewer patients experiencing profound LH suppression in the study group (7.14%, 16/224) than in the control group (14.29%, 32/224, $P < 0.05$). None of the patients in either group experienced a premature LH surge.

Serum E₂ levels increased consistently with the development of multiple follicles and were significantly higher in the control group than those in the study group at each observation point ($P < 0.01$).

In addition, the P level increased gradually during ovarian stimulation, especially on the day after trigger in the two groups. On the trigger day and the day after trigger, the P values in the study group were significantly higher than those in the control group ($P < 0.01$).

Pregnancy Outcomes After FET Cycles

In this study, 382 women completed a total of 574 FET cycles. A total of 189 patients completed 280 FET cycles in the MPA+hMG+ LE group, and 193 patients completed 294 FET cycles in the MPA + hMG group. Before the end of the study, 252 women completed one FET cycle, 83 women completed two FET cycles, 35 women completed three FET cycles, 9 women completed four FET cycles, 3 women completed five FET cycles, and the remaining 32 women did not complete FET cycles due to personal reasons. A total of 970 embryos were thawed, and the rate of viable frozen-thawed embryos was 100%. The implantation rate in the study group (42.14%, 201/477) was significantly higher than that in the control group (34.69%, 171/493) ($P < 0.05$). The clinical pregnancy rate, miscarriage rate and ectopic pregnancy rate were comparable between the two groups ($P > 0.05$). The live birth rate and neonatal status require further statistical analysis.

Discussion

This retrospective cohort study first evaluated the efficacy of PPOS protocols with or without letrozole in infertile women with PCOS. Our study showed that compared with PPOS protocol, letrozole supplementation could effectively improve the implantation rate and alleviate the profound pituitary suppression from progestin administration, but with a non-significant reduction in Gn consumption in women with PCOS undergoing IVF treatment.

The continuous supply of progestin in PPOS protocol can lead to strong pituitary suppression, presented as a sustained low level of LH during COH [7], which was also demonstrated by the present study. After combined letrozole treatment, the LH level kept steady in the first five days of treatment and then slowly declined until the trigger day. This may be related to the biological mechanism of letrozole, which can block oestrogen biosynthesis, thereby reducing negative oestrogenic feedback to the hypothalamic/pituitary axis and increasing the LH level[25]. Thus, the mean LH levels in the MPA+hMG+LE group were higher than those in the MPA + hMG group during the whole process of COH, and it follows that letrozole supplementation can release the pituitary from the deep inhibition of progestin. In addition, the large changes in LH levels (either an increase or decrease from basal levels) have been demonstrated to be associated with a decreased chance of clinical pregnancy [26]. Consistent with this, our present study also showed that relatively high levels and smaller changes in LH in the letrozole cotreatment with PPOS group were accompanied by an advanced implantation rate. While opposite conclusions also drawn that high follicular-phase LH levels appear to have a deleterious effect on the pregnancy outcome in women with PCOS [27]. Therefore, the optimal LH level required for the PPOS protocol in PCOS patients is still worth exploring.

Although letrozole alleviated the deep inhibitory effect of progestin on pituitary and improved LH levels during the COH, it does not interfere with the suppression of progestin on the premature LH surge. Indeed, there was no premature LH surge in either group of the present research. In rodent, hypothalamic GnRH/LH secretion is divided into GnRH/LH surge secretion, which is controlled by anteroventral periventricular (AVPV), and GnRH/LH pulse secretion, which is controlled by arcuate (ARC) nuclei, respectively[28]. Progestin's inhibitory effect on the GnRH/LH surge is mediated by AVPV [29], while letrozole plays a role to enhance LH pulse secretion through ARC in rodent [30]. The different action sites might explain why letrozole does not interfere with the blocking effect of progestin on LH surge. Whether this theory is applicable to humans still needs further exploration, as LH pulse and surge was regulated via different neuroendocrinology mechanisms in primate[28].

However, it should be mentioned that in our study, although letrozole coadministration with the PPOS protocol could significantly improve LH values in women with PCOS, the FSH levels were similar between the two groups during the COH. This may be related to the impaired steroid hormone feedback in females with PCOS[31, 32]. Hyperactive GnRH neuron in females with PCOS [33] result in partial pituitary desensitization, mainly manifested by a relative decline of FSH responsiveness [31, 32]. Because of this, the increase of FSH induced by LE through blocking oestrogen production[12] cannot be reflected in this study, and thus exogenous Gn consumption in both groups was comparable during the whole process of COH.

During oestrogen biosynthesis pathway, progesterone converts into androgen and then subsequently transformed into oestrogens by aromatase in brief[34]. As an aromatase inhibitor, letrozole coadministration results in decreased oestrogens and accumulation of precursors such as progesterone, testosterone as well as 17 α -progesterone [12, 34, 35]. Thus, the lower serum E₂ concentration and higher P levels were observed after cotreatment with LE in PPOS protocol. In addition, the accumulation of

androgens promotes recruitment of small antral follicles [36, 37]. Under the stimulation of exogenous Gn, the number of follicles with diameter >10 mm or >14 mm was significantly higher after LE coadministration, and more growing follicles may also result in higher progesterone levels in the late follicular phase during COH. However, the number of follicles that could reach the preovulation state may be similar although there were more follicles with diameter >10 mm, so comparable number of oocytes received was observed in both groups.

What we cannot ignore is that the rates of mature and fertilized oocytes were significantly lower in the study group, which may be related with the different follicles development mode between the two groups. After adding LE, higher LH level during the whole follicular phase in the study group probably advanced the dominant follicles selection[38], resulting in the polarization of the subsequent development of follicles. Thus, follicle sizes on the trigger day in the study group exhibit larger variation indicated by the B ultrasonic observation. Previous studies showed that patients with a greater proportion of their follicles within appropriate diameter range had more mature oocytes retrieved[39, 40]. Hence, a more disparate distribution of follicular size in the study group means that fewer follicular could reach this appropriate diameter range, which may lead to lower mature oocyte and fertilization rates. Nevertheless, in this follicle polarization development model, the dominant follicles may be more fully developed and could obtain high qualityoocytes[39, 40]. Moreover, higher progesterone level may also have a positive effect on oocyte development, which has been demonstrated in the previous study [36]. Therefore, the more developed of oocytes obtained, the better result of the implantation rate.

In our study, there was a waiting period between oocyte retrieval and embryo transfer as we used the “freeze-all” strategy, and 1462 extra embryos were not transferred, so we cannot show a complete data of pregnancy rates. Moreover, some women were less than three months pregnant, and some have not yet given birth, so we cannot provide data of ongoing pregnancy rates and live birth rate. Besides of that, this retrospective study may have potential unknown or unmeasured covariates, which may lead to incomplete or inexact matching and thus confound the robustness of the study findings. Prospective randomized controlled study with larger sample sizes and basic research should be performed in the future.

Abbreviations

IVF: In vitro fertilization; ICSI: Intracytoplasmic sperm injection; FET: Frozen embryo transfer; BMI: Body mass index; AFC: Antral follicle count; hCG: Human chorionic gonadotropin; FSH: Follicle stimulation hormone; LH: Luteinizing hormone; P: Progesterone; LE: Letrozole; MPA: Medroxyprogesterone acetate; OHSS: Ovarian hyperstimulation; PCOS: Polycystic ovarian syndrome; PPOS: Progesterone-primed ovarian stimulation

Declarations

Acknowledgments

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Authors' contributions

Yanping Kuang, Yali Liu and Sha Yu supervised the entire study, including procedures, conception, design, and completion. Qiuju Chen, Li Chen and Xiaoyan Mao were responsible for the collection of data. Jiaying Lin and Yali Liu analysed the data and drafted the manuscript together. Li Wang and Li Chen contributed to the data analysis and manuscript drafting. All authors participated in the ultimate interpretation of the study data and in revisions to the article. The authors have nothing to declare. The author(s) read and approved the final manuscript.

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Availability of data and materials

The data is not publicly shared and please contact author for data requests.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Shanghai Ninth People's Hospital (Institutional Review Board) (Number: SH9H-2021-T294-1).

Consent for publication

All patients have provided their consent for the data to be used for research and publications.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Flow chart of the study.

Figure 2

The dynamic changes in hormones during ovarian stimulation in the two groups The asterisk (*) represents $P < 0.05$ and (**) represents $P < 0.01$ at the time point.

Supplementary Files

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- [SupplementaryTable1.docx](#)