Flexible GnRH Antagonist Protocol *versus* Progestin-primed Ovarian Stimulation (PPOS) Protocol in Patients with Polycystic Ovary Syndrome: Comparison of Clinical Outcomes and Ovarian Response*

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Summary: Polycystic ovary syndrome (PCOS) is one of the most common causes of infertility in women. Progestin-primed ovarian stimulation (PPOS) protocol, which used oral progestin to prevent premature luteinizing hormone (LH) surges in ovarian stimulation, has been proved to be effective and safe in patients with PCOS. The aim of the present study was to compare the efficacy of PPOS protocol with that of the traditional gonadotropin-releasing hormone (GnRH) antagonist protocol in patients with PCOS. A total of 157 patients undergoing *in-vitro* fertilization (IVF) or intracytoplasmic sperm injection (ICSI) were recruited into this study. The patients were divided into two groups by the stimulation protocols: the GnRH antagonist protocol group and the PPOS protocol group. There was no significant difference in the clinical characteristics between the two groups. Dose and duration of gonadotropin were higher in the PPOS protocol group. Estradiol levels on the day of human chorionic gonadotropin (hCG) administration were significantly lower in the PPOS protocol group. Fertilization rates and the number of good quality embryos were similar between the two groups. Remarkably, we found 6 patients with moderate ovarian hyperstimulation syndrome (OHSS) in the GnRH antagonist protocol group but 0 in the PPOS protocol group. A total of 127 women completed their frozen embryo transfer (FET) cycles. There were no significant differences between the two groups in terms of clinical pregnancy rate per transfer, implantation rate, first-trimester miscarriage rate and on-going pregnancy rate per transfer. To conclude, PPOS protocol decreased the incidence of OHSS without adversely affecting clinical outcomes in patients with PCOS.
Key words: polycystic ovary syndrome; ovarian hyperstimulation syndrome; progestin-primed ovarian stimulation; GnRH antagonist protocol; controlled ovarian hyperstimulation

Polycystic ovary syndrome (PCOS) is the most common hormonal disorder in women and accounts for ≥80% of women with anovulatory infertility[1]. Worldwide prevalence of PCOS ranges from 4% to 21% of women on the basis of the different diagnostic criteria used[2, 3]. PCOS is diagnosed based on the Rotterdam criteria with two of three features such as anovulation, polycystic ovarian morphology on ultrasound scan and signs of clinical or biomedical hyperandrogenism (HA)[4]. Lifestyle intervention is recommended first in women who are obese largely on the basis of general health benefits. Bariatric surgery can be considered when the body mass index (BMI) is ≥35 kg/m^2 and lifestyle therapy has failed. Carefully conducted and monitored pharmacological ovulation induction can achieve good cumulative pregnancy rates. In addition, multiple pregnancy rates can be minimized with adherence to optimized protocols. Clomiphene citrate (CC) is used as first-line pharmacotherapy for ovulation induction. Letrozole appears to be a good alternative for ovulation induction in women with PCOS and CC resistance. Gonadotropins and laparoscopic surgery are used as second-line treatment. For patients who fail in lifestyle and ovulation induction therapy or have additional infertility factors, assisted reproductive technology (ART) represents the third line of treatment. Patients with PCOS are at a higher risk for ovarian hyperstimulation syndrome (OHSS) and therefore careful risk management strategies are required. Patients should be informed of the potential side effects of ovulation induction agents, the risk of IVF on the fetus and the risk of multiple pregnancies.

According to the World Health Organization (WHO) guidelines (Published in 2016), *in-vitro*

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fertilization (IVF) with the gonadotropin-releasing hormone (GnRH) antagonist protocol is the treatment of choice for patients with PCOS[5]. Compared to GnRH agonist protocol, GnRH-antagonist protocol can significantly reduce the incidence of OHSS without interfering with rates of clinical pregnancy and live birth[4]. Progestin-primed ovarian stimulation (PPOS) protocol is a new ovarian stimulation regimen based on a freeze-all strategy that uses progestin as an alternative to a GnRH analog for suppressing a premature LH surge during the follicular phase[6]. This new regimen of ovarian stimulation has been proved to effectively prevent a premature LH surge and does not compromise oocyte competence in cycles followed by embryo cryopreservation. It has been widely used in patients undergoing IVF since 2016 and showed good IVF outcomes[7, 8]. However there were no studies comparing the efficacy of PPOS protocol and GnRH-antagonist protocol in patients with PCOS. In this study, we compared the effects of these two protocols on the ovarian response and clinical outcomes in patients with PCOS undergoing IVF or ICSI.

1 SUBJECTS AND METHODS

1.1 Study Subjects

This study was approved by the Institutional Review Board (IRB) of Renmin Hospital, Wuhan University. A total of 157 patients with PCOS who were treated at the ART Centre, Renmin Hospital of Wuhan University, from May 2016 to October 2017, were evaluated in this study. Among them, 67 patients were treated with PPOS protocol and 90 patients were treated with the flexible GnRH-antagonist protocol. All of them were undergoing their first IVF cycle. PCOS was diagnosed based on the Rotterdam criteria with two of three features such as anovulation, polycystic ovarian morphology on ultrasound scan and signs of clinical or biomedical hyperandrogenism (HA)[4]. Women with other endocrine dysfunction or other indications for IVF were excluded from the study. All the patients included provided informed consent before study entry.

1.2 The PPOS Protocol

PPOS protocol was performed as previously described[9]. Patients in the PPOS group were given human menopausal gonadotropin (hMG) (Lizhu Pharmaceutical Factory, China) at a dose of 150 to 225 IU/day and medroxyprogesterone acetate (MPA) (Zhejiang Xianju Pharmaceutical Co., China) at a daily dose of 10 mg from day 3 of menstruation based on the results of the ultrasound and the blood tests. The dose of hMG was adjusted according to the patients' estradiol concentrations and ovarian responses. When three dominant follicles reached 18 mm in diameter, the final stage of oocyte maturation was induced by decapeptyl (0.2 mg) (Ferring International Center SA, Germany) and hCG (2000 IU) (Lizhu Pharmaceutical Factory, China).

1.3 The GnRH-antagonist Protocol

The flexible GnRH-antagonist protocol was performed as described previously[5]. Controlled ovarian hyperstimulation (COH) was started from day 2 of the menstruation using recombinant follicle-stimulating hormone (FSH) (Gonal-f; Merck Serono, Germany) alone or in combination with hMG (Lizhu Pharmaceutical Factory, China). The dose of Gn was adjusted according to estradiol concentrations and ovarian responses. When follicles with a mean diameter ≥14 mm were detected, a GnRH-antagonist (cetrorelix; Serono) was injected subcutaneously at a daily dose of 0.25 mg. When three dominant follicles reached 18 mm in diameter, the final stage of oocyte maturation was induced by decapeptyl (0.2 mg) (Ferring International Center SA, Germany) and hCG (2000 IU) (Lizhu Pharmaceutical Factory, China).

1.4 Oocyte Retrieval, Embryo Culture and Frozen-thawed Embryo Transfer

After 36 h, oocyte retrieval was performed under sedation and ultrasound guidance using a 16-G double-lumen aspiration needle. Oocyte insemination and embryo culture were performed according to standard procedures. Examination of embryo quality included the number/uniformity of blastomeres and the degree of fragmentation. Embryo morphology was scored according to The Istanbul Consensus Workshop[10]. OHSS was defined according to a previously published classification system[11].

All the good quality embryos (including grade A and B) were frozen by vitrification on the third day after oocyte retrieval. The embryos that were not of good quality were placed for further extended culture until the blastocyst stage. During this stage, only good morphology blastocysts (blastocyst better than grade 322) were cryopreserved.

Frozen-thawed embryos with >50% intact blastomeres were considered to have survived the freezing procedure. Only surviving embryos were transferred. Preparing endometrium for frozen-thawed embryo transfer (FET) cycles was performed as previously described[12]. Patients received progesterone supplementation until 10 weeks of pregnancy.

1.5 Statistical Analysis

All statistical analysis was performed using SPSS v16.0 (SPSS Inc., USA). Chi-squared test or Fisher's exact tests were used for categorical variables. One-way ANOVA was used for continuous variables. A P value <0.05 was considered to be statistically significant.

2 RESULTS

The baseline characteristics of patients are shown

in table 1 and the flow-up chart is shown in fig. 1. There was no significant difference between the PPOS group and the GnRH-antagonist group in terms of age, body mass index (BMI) and duration of infertility. The rate of the primary infertility was slightly higher in the PPOS group (53.73%) than in the GnRH-antagonist group (51.11%). But the difference was not significant. There were no significant differences in the baseline hormones including basal FSH, basal LH and basal E_2 between these two groups.

Ovarian responses between the two groups are shown in table 2. The PPOS group had a longer gonadotropin duration (10.40±1.78 *vs.* 9.11±1.55 days, $P<0.001$) and a higher dose of gonadotrophin (1971±576.67 *vs.* 1719.75±592.5 IU, $P<0.001$) than the GnRH-antagonist group. Compared with the GnRH-antagonist group, the estradiol levels on the day of HCG administration were significantly decreased in the PPOS group (3648±1838 *vs.* 4850±2538 pg/mL, $P<0.001$). Due to estradiol levels, the number of oocytes retrieved was significantly less in the PPOS group than in the GnRH-antagonist group (14.24±8.25 *vs.* 17.83±6.65, $P=0.049$). However, the number of 2PN fertilized oocyte, cleaved embryo, 2PN fertilization rate, and cleavage rate were similar between the two groups. In addition, there was no significant difference in the number of good-quality embryos between the two groups. The number of cryopreserved embryos was slightly greater in the GnRH-antagonist group than in the PPOS group (6.45±4.08 *vs.* 7.91±4.26, $P=0.048$). The cycle cancellation rate due to no viable embryos was similar between these two groups. Remarkably, no patients experienced mild-to-moderate OHSS in the PPOS group, but 6 patients in the GnRH-antagonist group developed moderate OHSS. The difference was significant (0 *vs.* 6.67%, $P=0.038$).

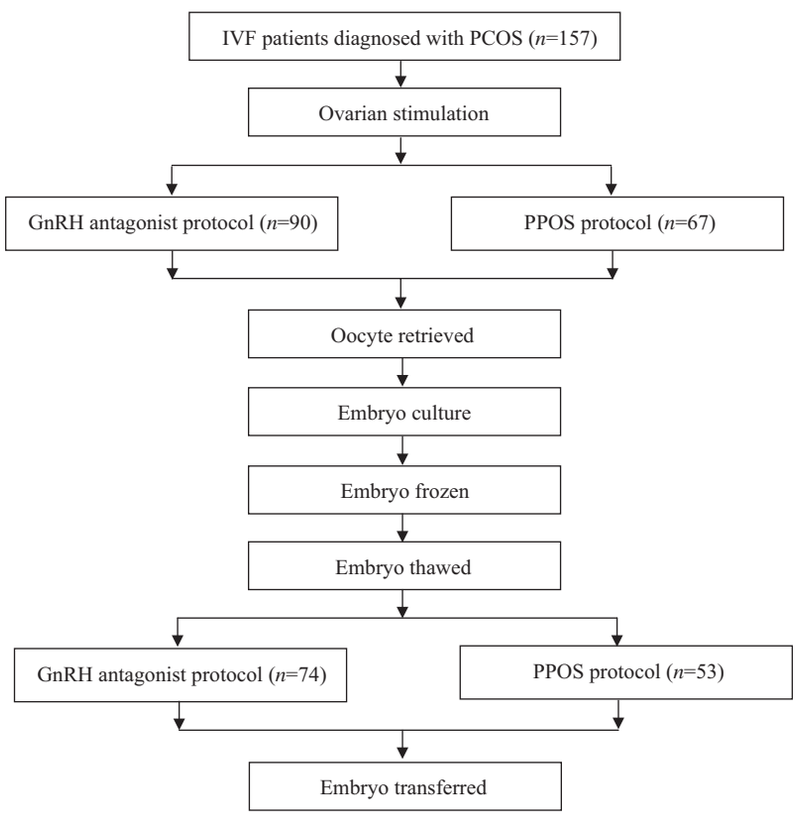

Fig. 1 Flow-up chart

Table 1 Baseline characteristics and hormonal profile of patients with PCOS undergoing IVF/ICSI Treatment

Parameter	PPOS protocol (hMG+MPA) (*n*=67)	GnRH antagonist protocol (*n*=90)	*P* value
Age (year)	32.31±4.62	30.69±3.99	NS
BMI (kg/m^2)	21.93±2.85	22.25±3.15	NS
Duration of infertility (year)	3.88±1.67	3.71±0.69	NS
Primary infertility, *n* (%)	35 (53.73%)	46 (51.11%)	NS
Basal FSH (IU/L)	6.14±1.73	6.53±2.86	NS
Basal LH (IU/L)	6.08±1.74	6.25±1.65	NS
Basal E_2 (ng/mL)	34.20±5.83	33.50±6.21	NS

Data are presented as mean±standard deviation unless otherwise specified. NS: not significant; hMG: human menopausal gonadotropin; MPA: medroxyprogesterone; BMI: body mass index; FSH: follicle stimulation hormone; LH: luteinizing hormone; E_2: Estradiol

The pregnancy outcomes after FET from the two groups are presented in table 3. A total of 127 women across the two groups completed a total of 127 FET cycles. All the patients completed the first FET cycle, including 53 from the PPOS group and 74 from the GnRH antagonist group. A total of 256 embryos were thawed. The rate of viable embryos after thawing was 99.61% (255/256). There were no significant differences between the two groups in the clinical pregnancy rate per transfer, the implantation rate of embryo, the first trimester miscarriage rate and the on-going pregnancy rate (OPR) per transfer. The rates of twin pregnancies and ectopic pregnancy rate were similar between these two groups.

3 DISCUSSION

In the present study, we aimed to determine whether the flexible GnRH antagonist protocol or the PPOS protocol is more suitable for patients with PCOS. To this end, we assessed the ovarian responses and the clinical outcomes in PCOS patients undergoing IVF. To our knowledge, there were no reports so far comparing the efficacy of these two protocols on the clinical outcomes in patients with PCOS.

PCOS is a highly prevalent disorder and a common cause of infertility among women. COH in PCOS remains a big challenge for fertility experts. OHSS and oocytes immaturity are the two major complications. GnRH antagonist protocol is a useful intervention in ART cycles to reduce OHSS rates (moderate-quality evidence)[13] and recommended by WHO as the treatment of choice for patients with PCOS undergoing IVF[5]. In the GnRH-agonist protocol, metformin reduces the risk of OHSS[5]. Interestingly, a recent study comparing the short GnRH antagonist protocol and the

Table 2 Comparison of ovarian stimulation characteristics between PPOS protocol and GnRH antagonist protocol

Parameter	PPOS protocol (hMG+MPA) (*n*=67)	GnRH antagonist protocol (*n*=90)	*P* value
Gn duration (day)	10.40±1.78	9.11±1.55	<0.001*
Gn dose (IU)	1971±576.67	1719.75±592.5	<0.001*
E_2 level at HCG day	3648±1838	4850±2538	<0.001*
Oocytes retrived (*n*)	14.24±8.25	17.83±6.65	<0.05*
2PN fertilized oocytes (*n*)	10.58±6.59	12.83±6.65	NS
Cleaved embryos (*n*)	10.18±6.38	12.41±6.51	NS
Good-quality embryos (*n*)	5.91±3.70	6.46±3.78	NS
Cryopreserved embryos (*n*)	6.45±4.08	7.91±4.26	<0.05*
2PN fertilization rate (%)	74.32%	71.96%	NS
Cleavage rate (%)	96.20%	96.71%	NS
Viable embryo rate per oocyte retrieved (%)	45.28%	44.36%	NS
Patients without vitrified embryos, % (*n*)	0 (0)	1.11 (1/90)	NS
Mild-to-moderate OHSS (%)	0 (0)	6.67% (6/90)	<0.05*

Data are presented as mean±standard deviation unless otherwise specified.
NS: not significant; MPA: medroxyprogesterone; Gn: gonadotropin; BMI: body mass index; FSH: follicle stimulation hormone; LH: luteinizing hormone; E_2: Estradiol; HCG: human chorionic gonadotropin; 2PN: two pronuclear; OHSS: ovarian hyper-stimulation syndrome; *P<0.05

Table 3 Pregnancy outcomes of frozen-thawed embryos between PPOS protocol and GnRH antagonist protocol

Parameter	PPOS protocol (hMG+MPA) (*n*=53)	GnRH antagonist protocol (*n*=74)	*P* value
Patients (*n*)	53	74	
FET cycles (*n*)	53	74	
Thawed embryos (*n*)	105	151	
Viable embryos after thawed (*n*)	105	150	
Transferred embryos (*n*)	1.98±0.37	2.02±0.33	NS
Mild stimulation (*n*)	29	40	
Hormone replacement therapy (*n*)	24	34	
Endometrial thickness (mm)	9.92±1.55	9.82±1.37	NS
Pregnancy outcome of FET (%)			
Clinical pregnancy rate per transfer	56.6% (30/53)	51.4% (38/74)	NS
Implantation rate	35.2% (37/105)	31.3% (47/150)	NS
First trimester miscarriage rate	6.67% (2/30)	10.53% (4/38)	NS
Twin pregnancy rate	23.3% (7/30)	23.7% (9/38)	NS
Ectopic pregnancy rate	0 (0/30)	2.63% (1/38)	NS
On-going pregnancy rate per transfer	52.83% (28/53)	44.59% (33/74)	NS

Data are presented as mean±standard deviation unless otherwise specified.
NS: not significant; MPA: medroxyprogesterone; FET: frozen-thawed embryo transfer

long GnRH agonist protocol found that women who were treated with the short GnRH antagonist protocol rated psychosocial and physical well-being during first ART treatment better than women who were treated with the long GnRH agonist[14].

PPOS is a new ovarian stimulation regimen for IVF. The advantages of PPOS include oral administration and better control over preovulatory luteinizing hormone (LH) levels. Progestin was used as an alternative to a GnRH analog for suppressing a premature LH surge during the follicular phase[15]. This new regimen of ovarian stimulation has been proved to effectively prevent a premature LH surge and does not compromise oocyte competence in cycles followed by embryo cryopreservation[6]. Assessing the safety of this novel regimen is an important premise for its routine practice. A large retrospective cohort study for infants born from IVF and embryo transfer cycles after either PPOS or the conventional gonadotropin-releasing hormone agonist short protocol was conducted recently. The birth characteristics regarding gestational age, birth weight and length, infant sex, and early neonatal death were comparable between the two groups. The incidence of live-birth defects in the PPOS group (1.52%) was similar to that in the short protocol group (1.63%). The study concluded that the neonatal outcomes and risk of congenital malformations were similar between the PPOS and conventional GnRH-a short protocol[16]. Because of its effectiveness and safety, the PPOS protocol has been accepted by IVF clinical worldwide and was widely used in patients defined as normal responders or poor responders and patients with PCOS since 2016 and showed amazing ovarian response and IVF outcomes[17–19].

GnRH antagonist protocol and PPOS protocol are highly comparable because of common characteristics: (1) both of them can significantly reduce the risk of OHSS; (2) both of them can greatly prevent the occurrence of premature LH peak; (3) freeze-all policy is suitable for the both protocols[20, 21]. To our knowledge, no studies have reported the comparison between the two protocols used in IVF cycles for patients with PCOS. Kuang *et al* compared cycle characteristics and endocrinological profiles using PPOS and GnRH-agonist short protocol for PCOS patients and found that PPOS protocol overcame premature ovulation and decreased the incidence of OHSS for patients with PCOS[9].

In our study, the 2PN fertilization rate, cleavage rate, number of good-quality embryos, viable embryo rate per oocyte retrieved, clinical pregnancy rate per transfer, implantation rate, and on-going pregnancy rate per transfer were similar between the PPOS protocol group and the GnRH antagonist protocol group. These results support that PPOS protocol is effective and feasible, without deteriorating the pregnancy outcomes. In addition, the total amount of gonadotrophin and the duration of gonadotrophin usage were significantly higher in the PPOS protocol group than in the GnRH antagonist group. One possible reason for this is that follicle becomes less sensitive to gonadotropin stimulation in the high progesterone and the pituitary suppression during the ovarian hyperstimulation in PPOS protocol[22].

Another highlight of this study is the low incidence of OHSS. Ideal management of PCOS patients would be the one that minimizes the patient's risk without compromising IVF cycle outcomes. In our study, the average E_2 levels at HCG day (3648±1838 pg/mL *vs.* 4850±2538 pg/mL, $P<0.001$) and the number of oocytes collected (14.24±8.25 *vs.* 17.83±6.65, $P<0.05$) in the PPOS protocol group were significantly decreased as compared with those in the GnRH antagonist protocol group. The PPOS protocol was associated with a low probability of mild-to-moderate OHSS (0 *vs.* 6.67%, $P<0.05$). Although the GnRH antagonist protocol produced more oocytes, the viable embryo rate per oocyte retrieved was nearly similar to that in the PPOS protocol.

Although the number of cryopreserved embryos was significantly higher in the GnRH antagonist protocol group (6.45±4.08 *vs.* 7.91±4.26, $P<0.05$), the cryopreserved embryos in the PPOS protocol group were enough for 2–3 transfers (1–3 embryos per transfer). The cumulative pregnancy rate per patient was similar[23, 24].

Major limitations of this study are the small patient population and the retrospective nature. Future studies with enlarged sample size are needed to generalize the findings from this study. A randomized controlled trial is needed to investigate whether the PCOS patients will benefit more from the PPOS protocol.

In conclusion, our study demonstrated that the PPOS protocol decreased the incidence of OHSS without adversely affecting pregnancy outcomes for patients with PCOS undergoing IVF. Long-term safety risks for children should be determined. Patients should be followed up for their genetic profiles.

Conflict of Interest Statement

The authors declare no potential conflicts of interest.

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