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Original Article

Progestin-primed ovarian stimulation is a feasible method for poor ovarian responders undergoing in IVF/ICSI compared to a GnRH antagonist protocol: A retrospective study

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ABSTRACT

Background: Poor ovarian response (POR) to ovarian hyperstimulation is one of the biggest challenges in assisted reproduction technology. The objective of this study was to compare the efficacy of progestin-primed ovarian stimulation (PPOS) with a GnRH antagonist (GnRH-ant) in poor ovarian response (POR) patients.
Materials and methods: This retrospective analysis included a total of 186 cycles of POR patients between 2014 and 2016. The patients were divided into two groups according to the method of stimulation protocol, as follows: 63 cycles were PPOS, and 123 cycles were GnRH-ant. Reproduction-related clinical outcomes in the two groups were compared.
Results: There were no significant differences in patients' age, dose and duration of gonadotropin (Gn) treatment, serum luteinizing hormone (LH) and E2 levels on the day of hCG injection, or the number of oocytes retrieved between the two groups. The MII oocyte rates, fertilization rates, good-quality embryo rates were significantly higher in the PPOS group than they were in the antagonist group ($p < 0.05$). In the subsequent frozen-thawed embryo transfer (FET), clinical pregnancy and live birth rates were significantly higher in the PPOS group than they were in the antagonist group ($p < 0.05$).
Conclusions: Compared with the GnRH-ant protocol, the PPOS protocol may be a better regime for POR that can effectively improve clinical pregnancy and live birth rates.
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Background

Poor ovarian response (POR) to ovarian hyperstimulation is one of the biggest challenges in assisted reproduction technology. POR has been reported to occur in 10% of women undergoing in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) [1]. The European Society for Human Reproduction and Embryology (ESHRE) defines a POR in IVF according to the presence of at least two of the following three features: (1) advanced maternal age or any other risk factor for POR, (2) a previous POR, and (3) an abnormal ovarian reserve test [2].

Several types of treatment are used in POR cases, including mild/minimal stimulation, GnRH antagonists (GnRH-ants) and GnRH agonists with a long protocol. The disadvantages of mild/minimal stimulation are the lower number of oocytes and higher cancellation rate, as this approach does not inhibit the premature luteinizing hormone (LH) surge. Therefore, GnRH analog cotreatment is often used to prevent a premature LH surge. Multiple studies have shown that there is no significant difference in the clinical pregnancy rate between the GnRH-ant protocol and GnRH agonist long protocol in POR patients [3,4], but the dose and duration of gonadotropin (Gn) treatment of the GnRH agonist protocol is higher than that of the GnRH-ant protocol.

The GnRH-ant regimen makes stimulation complex. Recently, Kuang et al. [5] found that medroxyprogesterone acetate (MPA) was an effective oral alternative for the prevention of premature LH surges in women undergoing controlled ovarian stimulation (COS) for IVF (called progestin-primed ovarian stimulation, PPOS). The pregnancy outcomes from frozen-thawed embryo transfer (FET) indicated that the embryos originating from human menopausal

Abbreviations: PPOS, progestin-primed ovarian stimulation; POR, poor ovarian response; IVF/ICS, in vitro fertilization/intracytoplasmic sperm injection; MPA, medroxyprogesterone acetate.

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gonadotropin (hMG) + MPA treatment cycles showed a similar developmental potential to embryos originating from the short protocol. Compared with GnRH-ants, MPA has the advantages of an oral administration route and providing easy access and more control over the LH levels. In hMG + MPA treatment cycles, the pituitary gland has not been desensitized by a GnRH agonist or antagonist.

Although many stimulation protocols have been established to improve clinical outcomes in POR patients, which protocol is the most effective remains controversial. The efficacy of PPOS in POR compared with that of conventional protocols is unclear. In this retrospective study, the aim is to compare the efficacy of PPOS and a GnRH-ant in POR patients.

Materials and methods

Study setting and patients

A retrospective analysis study was conducted at the Reproductive Medicine Center, First Affiliated Hospital of Guangxi Medical University, Nanning, China. Women undergoing IVF/ICSI regimens for the treatment of infertility were recruited between July 2014 and September 2016. All participants provided informed consent after counseling for infertility treatments and routine IVF procedures.

POR was defined when at least two of the following criteria were met: (1) age > 40 years, (2) prior history of poor response to conventional long treatment with GnRH agonists (three oocytes retrieved), and (3) a basal antral follicle count (AFC) <6. In addition, all patients had to have a body mass index between 18 and 28 kg/m^2, and frozen preservation of two or more embryos, with at least one good-quality embryo. The exclusion criteria were as follows: (1) patients with other gynecological conditions, such as endometrial polyps, intrauterine adhesions, or uterine submucosal myomas, that might cause endometrial abnormalities; (2) patients with adenomyosis; (3) patients with systemic diseases that indicated they could not tolerate pregnancy; and (4) patients who had hydropic fallopian tubes, PCOS, or stage III or higher endometriosis.

According to the different treatment protocols, the patients were divided into two groups, as follows: the PPOS group (63 cycles) and GnRH antagonist group (123 cycles). There were 50 cycles in the PPOS group and 112cycles in the GnRH antagonist group underwent subsequent FET using natural cycling for endometrial preparation.

Protocols for ovarian stimulation

The GnRH-ant protocol

The patients received intramuscular (IM) injections of 150–225 IU/d of recombinant follicle stimulating hormone according to the patient's weight (rFSH, Serono, Switzerland) for 5 days from the second or third day of the menstrual period; following this, the FSH dose was adjusted according to the ovarian response and E2 level. From the sixth day of FSH injection, 0.25 mg/d of cetrorelix acetate (Baxter Oncology GmbH, Westfalen, Germany) was subcutaneously injected until the day of hCG administration. When two dominant follicles reached a diameter of 18 mm, the final stage of oocyte maturation was induced with 10,000 IU of hCG.

The PPOS protocol

Patients in the study group were given hMG (Anhui Fengyuan Pharmaceutical Co, China) at a dose of 150–225 IU/day (according to the patient's weight) and MPA (Beijing Zhong Xin Pharmaceutical, China) at 10 mg/day from day 3 of menstruation. When two dominant follicles reached a diameter of 18 mm, the final stage of oocyte maturation was induced with 10,000 IU hCG.

Transvaginal ultrasound-guided oocyte retrieval was performed 36–37 h after triggering. Oocytes were fertilized using either conventional IVF or ICSI depending on the semen parameters. Examination of embryo quality included the number/uniformity of blastomeres and degree of fragmentation. Embryo morphology was scored according to the Cummins criteria [6].

All the good-quality embryos (including at least six blastomeres and fragments <50%) were frozen by vitrification on the third day after oocyte retrieval. The procedure of freezing and thawing cleavage-stage embryos and blastocysts has been described elsewhere [7].

The endometrial preparation protocol

For patients undergoing natural cycling, when the endometrial thickness reached ≥8 mm, follicular diameter was >18 mm, and serum luteotropic hormone (LH) was <20 IU/L, 10,000 IU of hCG (Li-Zhu, Zhuhai, China) was administered between 9 and 10 p.m. to trigger the final oocyte maturation. The thawed embryos were transferred 5 days later. When serum LH reached >20 IU/L, the same dose of hCG was administered in the afternoon, and FET was performed 4 days later. Progesterone treatment was commenced at 40 mg/day (Xianju, Zhejiang Province, China) 3 days before transplantation.

The maximum number of transferred embryos was two per patient. The progesterone supplementation was continued until 10 weeks of gestation after pregnancy was achieved.

Outcome variables

The primary analysis outcomes were the clinical pregnancy rates, abortion rates, serum LH and E2 levels on the day of hCG injection, MII oocyte rates, fertilization rates, good-quality embryos, and so on. Gestational sacs visible on ultrasonography were defined as clinical pregnancies. The spontaneous abortion rate was defined as pregnancy loss before 12 weeks' gestation.

Statistical analysis

The Statistical Package for Social Sciences (SPSS 13.0; IBM, Armonk, NY, USA) was used for data analysis. Descriptive statistical analyses were performed for each variable. Quantitative results are presented as the mean ± standard deviation (SD). Means were compared using analysis of variance. Proportions for the two groups were compared using the chi-square test. A value of $p < 0.05$ was considered to indicate statistical significance.

Results

There were no significant differences in the patients' age, dose and duration of Gn treatment, cycle cancellation rate, serum LH and E2 levels on the day of hCG injection, or number of oocytes retrieved between the two groups. The MII oocytes (87.50% vs. 66.70%), fertilization (80.25% vs. 66.54%), and good-quality embryo rates (70.00% vs. 54.66%) were significantly higher in the PPOS group than the antagonist group ($p < 0.05$). In the subsequent frozen-thawed embryo transfer (FET), the clinical pregnancy (38.00% vs. 22.32%) and live birth rates (32.00% vs. 17.86%) were significantly higher in the PPOS group than they were in the antagonist group ($p < 0.05$) (Tables 1–4).

Discussion

In the present study, we compared the clinical outcomes of PPOS and GnRH-ant in POR patients. There were no significant

Table 1
Baseline characteristics of patients.

	PPOS protocol	GnRH-ant protocol	*p*
Cycle	63	123	
Age (years)	41.35 ± 3.56	40.70 ± 3.55	0.24
Duration of infertility (years)	5.43 ± 3.83	6.18 ± 4.38	0.25
Basal FSH (IU/L)	14.23 ± 6.59	14.31 ± 3.97	0.93
AFC	3.10 ± 1.46	3.57 ± 1.65	0.06
BMI (kg/m^2)	22.37 ± 2.25	22.42 ± 4.49	0.08
Indication for IVF tubal factor (%)	83.87 (52/63)	81.3 (100/123)	0.83
Other (%)	17.5 (11/63)	18.7 (23/123)	0.83

Table 2
Comparison of clinical characteristics between the two groups.

	PPOS protocol	GnRH-ant protocol	*p*
Gn dose (IU)	2485.71 ± 1385.74	2140.93 ± 1036.01	0.06
Gn duration (days)	10.83 ± 5.02	9.90 ± 4.18	0.19
On hCG day LH (U/L)	1.78 ± 1.50	1.88 ± 1.70	0.20
On hCG day E2 (pg/mL)	560.03 ± 156.09	548.00 ± 170.00	0.31
On hCG day P (ng/mL)	0.73 ± 0.59	0.63 ± 0.68	0.21

Table 3
Comparison of embryonic laboratory indicators between the two groups.

	PPOS protocol	GnRH-ant protocol	*p*
No. of oocytes retrieved	1.81 ± 0.90	1.87 ± 1.25	0.73
MII oocyte rate (%)	87.5 (35/40)	66.7 (60/91)	0.01
Fertilization rate (%)	80.25 (65/81)	66.54 (173/260)	0.00
Good-quality embryo rate (%)	70 (42/60)	54.66 (88/161)	0.03
Cycle cancellation rate (%)	7.9 (5/63)	8.9 (11/123)	1.00

Table 4
Comparison of pregnancy outcomes between the two groups in FET.

	PPOS protocol	GnRH-ant protocol	*p*
Cycles	50	112	
Age (years)	40.35 ± 3.46	40.85 ± 3.45	0.23
Duration of infertility (years)	5.40 ± 3.73	6.08 ± 4.28	0.24
BMI (kg/m^2)	22.35 ± 2.24	22.43 ± 4.45	0.08
No. of transferred embryos	2	2	
Endometrial thickness (mm)	10.53 ± 2.78	10.34 ± 3.25	0.98
Clinical pregnancy rate (%)	38.00 (19/50)	22.32 (25/112)	0.038
Abortion rate (%)	15.78 (3/19)	20.00 (5/25)	0.072
Live birth rates (%)	32.00 (16/50)	17.86 (20/112)	0.045

differences in the dose and duration of Gn treatment, cycle cancellation rate, serum LH and E2 levels on the day of hCG injection, or number of oocytes retrieved between the two groups. The MII oocytes (87.50% vs. 66.70%), fertilization (80.25% vs. 66.54%), and good-quality embryo rates (70.00% vs. 54.66%) were significantly higher in the PPOS group than the antagonist group ($p < 0.05$). In the subsequent frozen-thawed embryo transfer (FET), clinical pregnancy (38.00% vs. 22.32%)and live birth rates (32.00% vs. 17.86%) were significantly higher in the PPOS group than they were in the antagonist group ($p < 0.05$). Compared with the GnRH-ant protocol, the PPOS protocol may be a better regime for POR.

A recent study by Kuang et al. [8] initiated ovarian stimulation with hMG and letrozole during the luteal phase and achieved satisfactory ovarian response and pregnancy outcomes. This study concluded that luteal-phase ovarian stimulation is feasible. In addition, the high plasma concentration of progestin enhances the negative feedback effects of estradiol, FSH, and LH secretion, which are suppressed to a low level in the luteal phase [9]. Boots's [10] review showed that ovarian stimulation initiated in the luteal phase does not compromise the quantity or quality of oocytes retrieved compared to the outcomes of traditional stimulation in the follicular phase. Based on this, in another study, Kuang et al. [5,11] administered hMG (150–225 IU) and MPA (10 mg/d) simultaneously in the follicular phase, beginning on cycle day 3, and improved its efficacy in terms of the low incidence of premature LH surge and comparable pregnancy outcomes with short protocols in infertile women with normal ovarian reserve and polycystic ovarian syndrome. Thus, they developed PPOS. The PPOS protocol breaks away from the tradition of relying on GnRH analogues (including GnRH agonists and GnRH-ants) to suppress the premature LH surge, providing a new option for preventing the untimely LH rise observed during IVF, in combination with the frozen-all strategy. In the present study, we also found that the PPOS can prevent the premature LH surge effectively in POR patients.

In Kuang et al.'s [5,11] reports, the doses of hMG administered in the PPOS group were significantly higher than those in the controls (short protocols) in women with a normal ovarian reserve and polycystic ovarian syndrome. One possible reason for the higher total amount of Gn units in the MPA group is associated with the pituitary suppression during the ovarian hyperstimulation. The incidence of OHSS was lower than those in the controls in the women with polycystic ovarian syndrome. In the present study, we found that the doses of Gn administered in the PPOS group were slightly higher than those in the controls, but the difference was not significant.

In the present study, we found that the MII oocyte, fertilization, and good-quality embryo rates in the PPOS group were significantly higher than those in the antagonist group ($p < 0.05$). Although there were no significant differences in clinical pregnancy and abortion rates between the two groups, the clinical outcome of the PPOS group was slightly better than that of the GnRH-ant group. In Kuang et al.'s [11] report, the fertilization and ongoing pregnancy rates per transfer were significantly higher in the PPOS group than controls ($p < 0.05$). These results indicate that PPOS protocols can improve the development potential of oocytes and embryos.

The advent of embryo and oocyte vitrification gives reproductive specialists an opportunity to consider new strategies for improving the practice and results of IVF attempts. As the freezing of entire cohorts does not compromise, and may even improve, the results of IVF attempts, it is possible to break away from the standard sequence of stimulation–retrieval–transfer. Thus, the constraints associated with ovarian stimulation in relation to the potential harmful effects of the hormonal environment on endometrial receptivity can be avoided. Epidemiological studies have shown better clinical outcomes in frozen embryo transfer cycles compared with fresh IVF cycles [12]. As a result, it is critical to collect more high-quality oocytes for subsequent embryo transfer in POR cases, since the lower number of oocytes is the major issue for POR.

In this study, we achieved higher MII oocyte, fertilization, good-quality embryo rates and higher live birth rates in the PPOS protocol than the GnRH-ant protocol. Moreover, MPA was a simple, convenient, effective, and cheap treatment that could be delivered orally. Thus, the PPOS protocol may be a better regime for POR patients. Massin [13] used endogenous and exogenous progesterone to block the LH surge during ovarian stimulation for IVF as a new stimulation regimen. Such new regimens enable more flexibility and are of emerging interest in daily practice.

This study had some limitations. First, this was a retrospective study; in future work, the comparison of ovulation induction characteristics between the PPOS and GnRH-ant approaches should be further investigated in well-designed, prospective randomized controlled clinical trials. Second, the cumulative pregnancy must be included in subsequent studies. In addition, further research is required to determine whether this method can be successfully applied to patients of advanced maternal age or low responder patients.

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Conflict of interest

The authors declare that they have no conflict of interest.

Availability of data and materials

The data analyzed during the current study are available from the Reproductive Medicine Center of the first affiliated Hospital of Guangxi Medical University.

Author's contributions

Pinxiu Huang and Minling Tang: data collection, Manuscript writing, these authors contributed equally to this work and should be considered co-first authors; Aiping Qin: the correspondence author, guide planning.

Ethics approval

This work approved by the ethics committee of the first affiliated Hospital of Guangxi Medical University.

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