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Original Article

Luteal-phase ovarian stimulation is a feasible method for poor ovarian responders undergoing *in vitro* fertilization/intracytoplasmic sperm injection-embryo transfer treatment compared to a GnRH antagonist protocol: A retrospective study

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ABSTRACT

Objective: Poor ovarian response to ovarian hyperstimulation is one of the biggest challenges in assisted reproduction technology. Although many stimulation protocols have been established to improve clinical outcomes in poor ovarian responders (PORs), which protocol is the most effective remains controversial. Luteal-phase ovarian stimulation (LPOS) has been used in normal ovarian responders with satisfactory outcomes. However, the efficacy of LPOS in PORs is unclear. This study aimed to compare the efficacy of LPOS and GnRH antagonist (GnRH-ant) in PORs.

Materials and methods: The clinical parameters in PORs who received LPOS (50 cycles in 39 patients) or GnRH-ant (158 cycles in 123 patients) were compared.

Results: Compared with those in the GnRH-ant group, the PORs in the LPOS group showed significantly fewer basal antral follicles (3.1 ± 2.2 vs. 4.1 ± 1.6, $p < 0.001$) and a higher *in vitro* fertilization rate. There were no significant differences in the numbers of retrieved oocytes and D3 transferable embryos between the two groups. However, the pregnancy rate in the LPOS group (46.4%) was significantly higher than that in the GnRH-ant group (25.8% overall; 22.9% from fresh embryos and 29.6% from frozen embryos). Moreover, 23 PORs in the LPOS group underwent oocyte retrieval twice in one cycle, and the numbers of retrieved oocytes and transferable embryos from the luteal phase were significantly higher than those from the follicular phase in the same menstrual cycle.

Conclusions: Compared with the GnRH-ant protocol, the LPOS protocol may be a better regime for PORs that can increase the numbers of retrieved oocytes and transferable embryos as well as the pregnancy rate.

Introduction

Assisted reproduction technology such as *in vitro* fertilization–embryo transfer (IVF–ET) has helped millions of subfertile females to have their own babies, and ovarian stimulation is considered to be the critical factor for clinical outcomes. Poor ovarian response (POR) to controlled ovarian hyperstimulation is one of the biggest challenges in assisted reproduction technology and has been reported to occur in 9–24% of women undergoing IVF [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]. Many stimulation protocols have been established to improve clinical outcomes in PORs. Although many related studies have been published, which protocol is the most effective and preferable in PORs remains controversial [3–5].

It is well accepted that only one follicle is selected to mature in each menstrual cycle, whereas the others undergo atresia [6]. Standard regimens of ovarian stimulation in IVF usually start from

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the early follicular phase of the menstrual cycle, but follicular-phase ovarian stimulation can cause serious complications such as ovarian hyperstimulation syndrome, premature luteinization, and suboptimal oocyte quality [3,4,7]. Therefore, GnRH analog cotreatment is often used to prevent the premature l*uteinizing hormone (*LH) surge; however, this regimen makes the stimulation complex [7]. Interestingly, some studies have demonstrated that small antral follicles observed during the luteal phase may not necessarily undergo atresia but instead remain in the early stages of follicular development [8,9]. The detection of oocyte and granulosa cell viability implicates the presence of healthy follicles in the luteal phase. Previous studies demonstrated that the oocytes retrieved during the luteal phase can be competent to mature and be fertilized [10,11], which implicates the possibility that follicles are continuously available for stimulation by Gn (gonadotropin) during the menstrual cycle. Moreover, a recent study by Kuang et al [12] initiated ovarian stimulation with hMG (human menopausal gonadotropin) and letrozole during the luteal phase and achieved satisfactory ovarian response and pregnancy outcome. This study concluded that luteal-phase ovarian stimulation (LPOS) is feasible for producing competent oocytes in women undergoing IVF/intracytoplasmic sperm injection (ICSI) treatment [12]. However, the efficacy of LPOS in PORs compared with that of conventional protocols is unclear. In this retrospective study, we compared the clinical data from PORs who received LPOS or GnRH antagonist treatment at our center and further compared the quality of oocytes retrieved during the luteal phase and follicular phase in the same patient.

Materials and methods

Patients

Data were collected for a total of 162 PORs who underwent IVF/ICSI treatment at the Assisted Reproduction Center of Liuzhou Maternal & Child Health Hospital (Liuzhou, Guangxi, China) from May 2013 to May 2014. This study was approved by the local ethics committee of Liuzhou Maternal & Child Health Hospital, and oral consent was obtained from all patients.

PORs were 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 agonist ($\leq$3 oocytes retrieved), and (3) basal antral follicle count (AFC) <6. Also, all patients had to have a body mass index between 18 and 28 kg/m^2 and be without endometriosis and hydrosalpinx. According to different treatment protocols, the patients were divided into two groups: the LPOS group (50 cycles, 39 patients) and the GnRH antagonist group (158 cycles, 123 patients) (Figure 1).

Protocols for ovarian stimulation

LPOS group

LPOS was carried out according to a previously described protocol [13]. Briefly, on the next day of oocyte retrieval (or advanced ovulation) after mild stimulation or natural cycle, patients with follicles <10 mm received 225 IM (intramuscular) hMG (Livzon Pharmaceutical Group Inc., Zhuhai, China) and 2.5 mg/d oral Letrozole (LE, Jiangsu Hengrui Medicine Co. Ltd., Lianyunguang, China) or 50 mg/d oral clomifene citrate (CC; Codal Synto Pharmaceuticals, Limassol, Cyprus). The initial follicular monitoring started 5–7 days later and was performed every 2–4 days by transvaginal ultrasound examination to record the number of developing follicles and measurement of serum follicle-stimulating hormone (FSH), LH, estradiol, and progesterone (P) concentrations. LE/CC administration was stopped when the dominant follicles reached 12 mm in diameter. Daily administration of 10 mg medroxyprogesterone acetate was added beginning on stimulation Day 12 for cases in which the post-ovulation follicle size was smaller than 14 mm in diameter and the stimulation needed to continue for several more days. When three dominant follicles reached a diameter of 18 mm or one dominant follicle exceeded 20 mm in diameter, the final stage of oocyte maturation was induced via an injection of 10,000 IU human chorionic gonadotrophin (hCG).

For the mild stimulation protocol, the PORs received 2.5 mg/d oral LE or 50 mg/d oral CC for 5 days from the 2nd or 3rd day of the same menstrual period, followed by IM injection of 75–150 IU/d hMG until the day of GnRH agonist (0.1 mg Diphereline; Ipsen Pharma Biotech, Signes, France) administration to induce oocyte maturation once there were three dominant follicles with a diameter of 18 mm or one dominant follicle exceeding 20 mm in diameter (Figure 2).

GnRH-ant group

The patients received IM injections of 150–225 IU/d hMG for 5 days from the 2nd or 3rd day of the menstrual period, and then the hMG dose was adjusted according to the ovarian response and E2 level. From the 6th day of hMG injection, 0.25 mg/d cetrorelix acetate (Baxter Oncology GmbH, Westfalen, Germany) was subcutaneously injected until the day of hCG administration. When three dominant follicles reached a diameter of 18 mm or one mature dominant follicle exceeded 20 mm in diameter, the final stage of oocyte maturation was induced with 10,000 IU hCG.

Oocyte retrieval and fertilization

Transvaginal ultrasound-guided oocyte retrieval was conducted 36–37 hours later after maturation inducement. In 27 cycles in patients in the LPOS group, oocytes were retrieved at the follicular phase and the luteal phase, whereas in another 23 cycles, oocytes were only obtained at the luteal phase (with advanced ovulation in the follicular phase). Fertilization was carried out *in vitro*, by either conventional insemination or ICSI, depending on semen parameters. Successful fertilization was defined when two clear pronuclei were present after 16–18 hours of insemination.

Embryo culture and transfer

The fertilized oocytes were cultured with G1.5 and G2.5 sequential media (Vitrolife, Kungsbacka, Sweden) at 37°C with 6% CO_2 and 5% O_2. On the 3rd day of fertilization, embryos were graded according to the number and regularity of blastomeres and the degree of embryonic fragmentation from Cummins's criteria [14]. The high-quality embryos (grades 1 and 2) were transferred freshly or frozen by vitrification on the 3rd day. If the embryos were not of top quality, they were continuously cultured until the blastocyst stage. On Day 5 or 6, the quality of blastocysts was scored according to the Gardner blastocyst grading system. At this stage, the blastocysts with >3BB grade were considered high quality, whereas the blastocysts with >3CC grade were transferred or frozen.

ET in the GnRH-ant group was conducted on the 3rd or 5th day (if a high-quality embryo was not available on Day 3). For ET in the LPOS group, all available embryos were frozen. The procedure for freezing and thawing embryos was carried out as previously described [15]. Endometrial preparation and frozen ET were performed in either a natural cycle or a stimulation cycle or a hormone replacement therapy (HRT) cycle. For endometrial preparation in the HRT cycle, oral 4–6 mg/d E2 (Bayer Pharma AG, *Berlin, Germany*) was given from cycle Day 3 onward. Once the endometrial

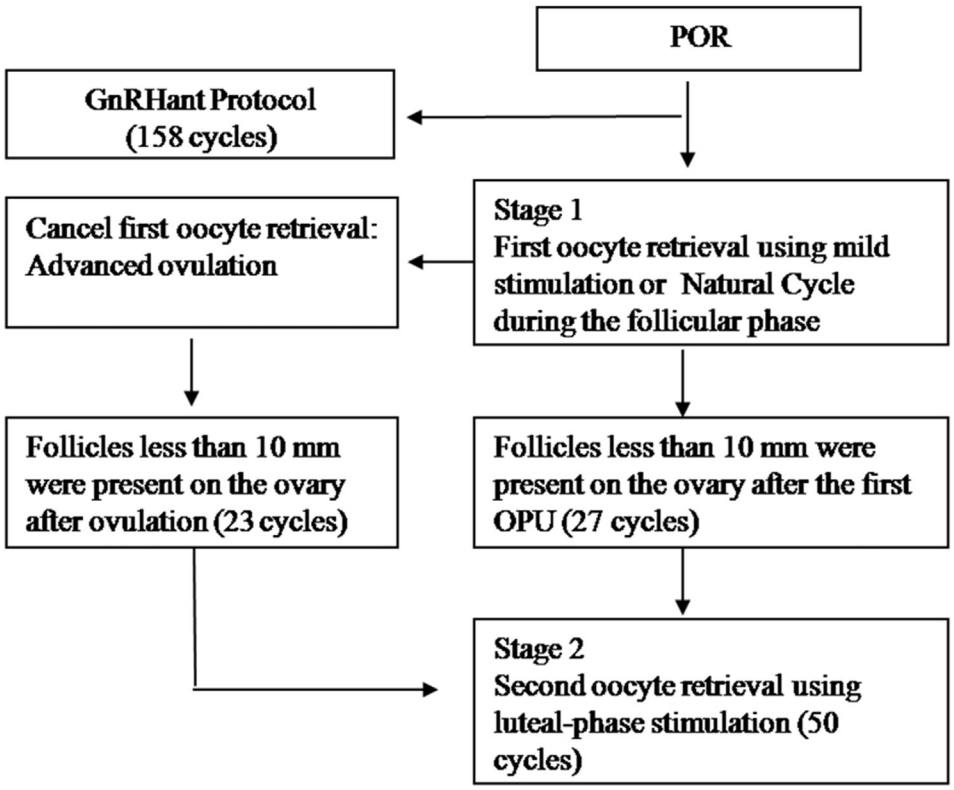

Figure 1. Profile summary of the pilot study. GnRH-ant = gonadotrophin-releasing hormone antagonist; POR = poor ovarian response.

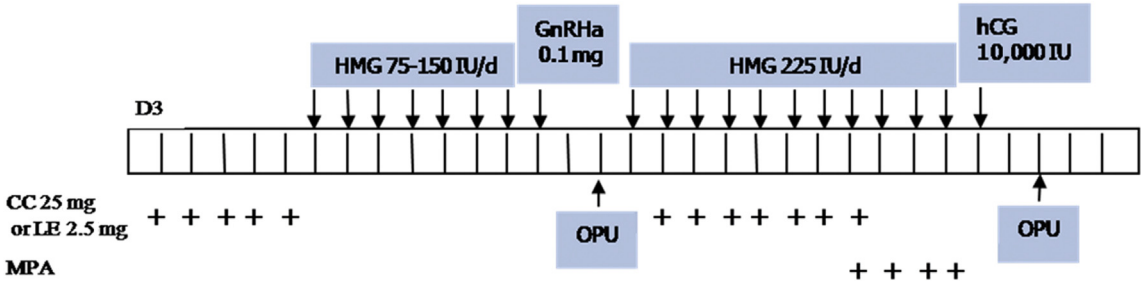

Figure 2. The protocols for mild stimulation and luteal phase ovarian stimulation in patients with poor ovarian response. CC = clomiphene; GnRH-a = gonadotrophin-releasing hormone agonist; hCG = human chorionic gonadotrophin; HMG = human menopausal gonadotrophin; LE = letrozole; MPA, medroxyprogesterone acetate; OPU = ovum-pick-up.

lining was ≥8 mm thick, 60 mg/d P in oil was administered IM until Day 14 after ET, and ET was carried out on Day 4 or 6 after P injection. The maximum number of transferred embryos was three per patient. After ET in both groups, IM injection of 40 mg/d P (natural cycle, stimulation cycle) or 60 mg/d P (HRT cycle) was started. The outcome of pregnancy was first examined on Day 14 after ET by measuring the blood hCG level and further verified on Day 35 after ET by ultrasound. If pregnancy was achieved, P injection was continued until 8–10 weeks of gestation.

Statistical analysis

The data were analyzed using SPSS 13.0 software, and some data were presented as the mean ± standard deviation. The significance of clinical parameters between two groups was analyzed using Chi-square test or Fisher's exact tests. Moreover, continuous variables were analyzed by independent or paired *t* tests. A p value <0.05 was considered statistically significant.

Results

Comparison of clinical parameters between LPOS and GnRH-ant groups

There were no significant differences in patients' age, body mass index, years of infertility, basal FSH levels, LH levels, and E2 levels (Table 1). The basal AFC in the LPOS group was significantly lower than that in the GnRH-ant group. On the day of hCG administration, compared with those in the GnRH-ant group, PORs in the LPOS group showed significantly reduced LH and increased P, but similar levels of FSH and E2. None of PORs in the LPOS group had LH ≥ 10 IU/L, whereas 9.5% (15/158) of PORs in the GnRH-ant group exhibited LH ≥ 10 IU/L. The total amount and days of Gn administration in the LPOS group were significantly greater than those in the GnRH-ant group, but there was no significant difference in the number of retrieved oocytes between the two groups (Table 1). After ovarian stimulation, compared with GnRH-ant group, the rate

Table 1
Comparison of clinical parameters in the luteal-phase ovarian stimulation (LPOS) and GnRH antagonist (GnRH-ant) groups.

Group	LPOS ($n = 50$)	GnRH-ant ($n = 1$ 58)	p
Baseline parameters			
Age (y)	36.1 ± 4.4	36.7 ± 4.7	0.42
Duration of infertility (y)	6.1 ± 4.2	5.6 ± 4.0	0.43
BMI (kg/m^2)	21.1 ± 3.8	21.6 ± 3.2	0.89
Cycles of previous treatment	2.3 ± 1.4	2.0 ± 1.3	0.16
Basal AFC	3.1 ± 2.2	4.1 ± 1.6	<0.001*
Basal serum FSH (IU/L)	9.8 ± 4.8	10.5 ± 5.2	0.42
Basal serum LH (IU/L)	4.6 ± 3.3	4.4 ± 3.4	0.60
Basal serum E2 (pg/L)	67.7 ± 69.8	54.4 ± 27.8	0.20
Duration of stimulation (d)	9.3 ± 4.3	7.7 ± 2.6	0.02*
Total Gn consumption (tube)	27.6 ± 12.8	19.6 ± 9.1	<0.001*
Hormone levels on the day of hCG administration			
FSH (IU/L)	17.6 ± 5.5	17.9 ± 6.0	0.76
LH (IU/L)	3.0 ± 2.6	4.9 ± 5.2	<0.001*
E2 (pg/L)	1247.8 ± 1015.8	919.4 ± 571.7	0.21
P (ng/L)	12.8 ± 14.5	0.81 ± 0.85	<0.001*
Ratio of LH ≥ 10 IU/L	0	9.5%	0.026*
Outcome of ovarian stimulation			
COCs retrieved	5.2 ± 5.6	4.0 ± 2.6	0.14
Rate of oocyte retrieval (%)	69.5	75.1	0.04*
Ratio of IVF/ICSI application (%)	80.0/20.0	82.3/17.7	0.72
Maturation rate in ICSI (M II, %)	79.2	83.5	0.50
Fertilization rate by ICSI (%)	86.8	83.8	0.65
Fertilization rate by IVF (%)	79.4	69.7	0.01*
D3 embryos available	3.3 ± 4.3	2.2 ± 1.7	0.08

The data are presented as mean ± SD. Basal AFC and basal FSH, LH and E2 levels were measured on the 2nd to 5th days of the menstrual period. The data related to oocyte/embryo parameters in the LPOS group were from the luteal phase. The percentage data were analyzed by Chi-square test or Fisher's exact test, whereas other data were analyzed with independent t test. *$p < 0.05$.
AFC = antral follicle count; BMI = body mass index; COCs = cumulus oocyte complexes; E2 = estradiol; FSH = follicle stimulating hormone; Gn, gonadotropin; ICSI = intracytoplasmic sperm injection; IVF = *in vitro* fertilization; LH = luteinizing hormone; P = progesterone.

of oocyte retrieval was significantly reduced, but the fertilization rate by IVF was significantly increased in the LPOS group (Table 1). There were no significant differences in the fertilization rate by ICSI or in the number of transferable embryos between the two groups (Table 1). More importantly, the pregnancy rate in the LPOS group (46.4%) was significantly higher than that in the GnRH-ant group (overall, 25.8%; $p = 0.04$) with the use of fresh embryos (22.9%, $p = 0.03$) as well as frozen embryos (29.6%, $p = 0.15$) (Table 2). There were no significant differences in the implantation rate of D3 or D5 embryos, and the miscarriage rate between the two groups (Table 2).

Comparison of clinical parameters of oocytes retrieved during the follicular phase and luteal phase

To further verify the efficacy of the LPOS protocol, we compared the clinical characteristics of oocytes retrieved during the follicular phase using mild stimulation and the luteal phase in the same cycle of PORs undergoing LPOS treatment. There were no significant differences in the rates of maturation, fertilization, implantation, and pregnancy between the follicular phase and luteal phase ($p > 0.05$, Table 3). However, the numbers of retrieved oocytes and transferable embryos from the luteal phase were significantly higher than those from the follicular phase ($p < 0.05$, Table 3).

Discussion

In the present study, we compared the clinical outcomes of LPOS and GnRH-ant regimes in PORs. Although the AFC in the LPOS group was significantly lower than that in the GnRH-ant group, the numbers of retrieved oocytes and transferable embryos were not significantly different between the two regimes. More importantly, the pregnancy rate in the LPOS group was significantly higher than that in the GnRH-ant group. These data indicate that LPOS is a feasible and possibly better regimen for the treatment of PORs compared to the GnRH-ant protocol.

The wave theory of follicle development proposes that antral follicles at the luteal phase may not regress, but instead develop to maturity after appropriate stimulation. This possibility has been verified in animals and humans [10,16]. Recently, Kuang et al [12] reported that the clinical pregnancy rate, ongoing pregnancy rate, and implantation rate of frozen embryos obtained from LPOS were 55.46%, 48.91%, and 40.37%, respectively, in normal response women, and 56.5% (13/23), 47.8% (11/23), and 36.6% (15/41), respectively, in PORs who underwent double stimulations (follicle phase stimulation and luteal phase stimulation) within one menstrual cycle [13]. These data suggest that LPOS is feasible for infertile women, especially for PORs.

Table 2
Comparison of clinical outcomes of embryos from LPOS and GnRH-ant protocols.

	LPOS (first FET)	GnRH-ant	
		Fresh embryo transfer	First FET
Cancellation rate (no available embryos) (%, n)	17.9 (7/39)	16.3 (20/123)	
Number of PORs with embryos transferred	28	70	54
Ratio of transferred embryos on Day 3/Day 5 (%)	85.7/14.3	100/0	88.9/11.1
Embryos transferred	2.1 ± 0.5	2.0 ± 0.6	2.1 ± 0.6
Implantation rate (%, n)			
D3 embryos	23.5 (12/51)	12.9 (18/140)	16.0 (16/100)
D5 embryos	50.0 (4/8)	—	18.2 (2/11)
Clinical pregnancy rate (%, n)	46.4 (13/28)	22.9 (16/70)*	29.6 (16/54)
Spontaneous abortion rate (%, n)	15.4 (2/13)	25 (4/16)	6.3 (1/16)

The data are presented as mean ± SD or ratio. The percentage data were analyzed by Chi-square test or Fisher's exact test, whereas number of transferable embryos was analyzed with independent t test. *$p < 0.05$ compared with LPOS.
FET = frozen embryo transfer; GnRH-ant = GnRH antagonist; LPOS = luteal-phase ovarian stimulation; PORs = poor ovarian responders.

Table 3
Comparison of clinical parameters and outcomes of oocytes/embryos from the follicular phase using mild stimulation and the luteal phase in one cycle.

	Follicular phase ($n = 23$)	Luteal phase ($n = 23$)	p
Outcome of ovarian stimulation			
Rate of oocyte retrieval (%)	69.8	63.0	0.40
COCs retrieved	1.6 ± 1.1	3.5 ± 3.4	0.01*
Maturation rate in ICSI (%, n)	33.3 (1/3)	77.8 (7/9)	0.24
Fertilization rate by ICSI (%, n)	100.0 (1/1)	100 (7/7)	/
Fertilization rate by IVF (%, n)	76.5 (26/34)	73.2 (52/71)	0.72
Clinical outcome			
Embryos transferred	2.0 ± 0	2.1 ± 0.3	0.40
Implantation rate (%, n)	25 (1/4)	28.0 (7/25)	1.00
Clinical pregnancy rate (%, n)	50.0 (1/2)	33.3 (4/12)	1.00
Spontaneous abortion rate (%)	0	0	

The percentage data were analyzed by Chi-square test or Fisher's exact test, whereas other data were analyzed with independent t test.
*$p < 0.05$.
COCs = cumulus oocyte complexes; ICSI = intracytoplasmic sperm injection; IVF = *in vitro* fertilization.

LPOS could induce synchronous growth of a group of follicles. The conventional protocols usually start during the menstrual period and easily cause nonsynchronous growth of follicles [3,5]. In the luteal phase, the P and inhibin A secreted from the corpus luteum can inhibit the development of a dominant follicle, but exogenous Gn can induce synchronous growth of a group of follicles [17]. Thus, ovarian stimulation in the luteal phase may achieve a greater number of high-quality oocytes. This may help to explain why a significantly lower AFC number was observed in the LPOS group, but the numbers of oocytes retrieved and available embryos were similar to those in the GnRH-ant group in our study. In addition, the LH peak is not present after LPOS treatment. In the conventional protocols for ovarian stimulation, hCG administration must be given prior to the LH surge, and thus, the LH level must be carefully monitored [3,4]. Compared with the conventional GnRH-ant protocol, the LH level in the LPOS group was significantly reduced; 9.5% of PORs in the GnRH-ant group had an LH $\geq$10 IU/L compared to none in the LPOS group. Therefore, it is easier to control hCG administration and oocyte retrieval in the LPOS regime. Importantly, the LPOS procedure allows us to retrieve oocytes twice in one cycle. The lower number of oocytes is the major issue in PORs, and thus, it is critical to collect more high-quality oocytes for subsequent embryo transfer.

In this study, we retrieved more oocytes from LPOS-treated PORs, but the rate of oocyte retrieval in the LPOS group was significantly lower than that in the GnRH-ant group. Although our finding is similar to that reported in Kuang et al's study (65.5%) [12], the possible reason for the lower rate of oocyte retrieval is associated with repeated oocyte retrieval in one cycle, because the corpus luteum cysts formed after oocyte retrieval in the follicular phase will be easily considered as follicles during oocyte retrieval in the luteal phase. However, there are a few limitations in this study. First, this is a retrospective study, and all findings need to be verified in perspective studies with a large cohort of PORs. Second, we used two different medicines in the LPOS procedure, which makes the procedure complex. Third, epidemiologic studies have shown better clinical outcomes in frozen embryo transfer cycles compared with fresh IVF cycles, because multiple corpus lutea may secrete high levels of hormones and other factors that can affect the endometrium and the implanting embryo during a fresh IVF cycle [18]. In our study, we compared frozen embryos to fresh embryos, which may be a bias of the data. Additionally, the cancelation rate was similar between the two groups owing to a lack of transferable embryos.

In conclusion, compared with the conventional GnRH-ant protocol, the LPOS protocol can increase the numbers of retrieved oocytes and transferable embryos as well as the pregnancy rate. Thus, LPOS may be a better procedure for PORs.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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