Comparison of Progestin-Primed Ovarian Stimulation Regimen and Antagonist Regimen in Diminished Ovarian Reserve Patients Over 35 Years of Age

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Research Article

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Abstract

Background

the aim of this study was to compare the efficacy of progestin-primed ovarian stimulation (PPOS) regimen and GnRH antagonist regimen in infertile patients older than 35 years with diminished ovarian reserve (DOR).

Methods

a retrospective cross-sectional study of 196 in vitro fertilization (IVF) cycles between January 2016 and January 2020 was performed. The measured outcomes included the number of retrieved oocytes, incidence of premature LH surge, laboratory indicators and frozen embryo transfer (FET) outcome.

Results

the number of oocytes retrieved in the antagonist group was higher than those in the PPOS group ($p < 0.05$). Incidence of premature LH surge in two groups showed no difference ($p > 0.05$). E2 and P on HCG administration day of antagonist group were higher than those of PPOS group ($p < 0.05$). And there was no significant difference between two groups of FET outcome indicators ($p > 0.05$).

Conclusions

for DOR patients over 35 years of age, antagonist regimen would retrieve more oocytes than PPOS regimen. Therefore, from the perspective of oocyte retrieving, the antagonist regimen might be more suitable for DOR patients over 35 years old.

Background

Diminished ovarian reserve (DOR) refers to the phenomenon that the number and quality of oocytes decrease with age [1], which has been one of a major challenges in the treatment of infertility [2]. One of the main reasons why patients undergoing assisted reproductive technology (ART) have poor responses to the ovaries is DOR [3, 4]. These infertile patients are less likely to get pregnant through in vitro fertilization (IVF) treatments [5]. The American Association for Obstetrics and Gynecology (ACOG) has pointed out that women who have fertility requirements, are older than 35 years old and have not been pregnant within six months, are at high risk of DOR [6]. Therefore, infertile women with DOR older than 35 years of age should be paid particular concern.

Controlled ovarian stimulation (COS) is a key step in the IVF treatments [7]. This step is even more crucial for patients with DOR. During the ovarian stimulation, premature luteinizing hormone (LH) surge was

considered to be one of the important causes affecting the number of retrieved oocytes and the cycle cancellation [8]. Therefore, suppression of the pituitary gland during COS is particularly important for IVF outcomes. Conventional protocols cannot effectively inhibit the premature LH surge. In the last decade, antagonists are commonly used in ovulation induction programs. It can suppress premature LH surge and reduce the risk of ovarian hyperstimulation syndrome (OHSS) [9]. It was precisely because of the emergence of 'freeze-all' strategies, Kuang et al. [10] proposed the progestin-primed ovarian stimulation (PPOS) protocol of progesterone combined with Gonadotrophin-releasing hormone (GnRH) in the early stage of follicular development. As a new protocol that has been used for the last few years, the PPOS protocol also has the advantages of preventing premature LH surge. The replacement of oral progesterone with multiple injections of GnRH analogues also reduces the suffering of patients [11].

Both protocols can inhibit the premature LH surge, but they have their own advantages and disadvantages. There was no conclusive decision on which effect was better. In elderly patients with DOR, the use of antagonist regimens might also be accompanied by the appearance of premature LH surge [12]. Although the PPOS protocol had been proved that it could prevent premature ovulation in DOR patients [13], there was no research only for patients over the age of 35. This study intended to compare the efficacy of GnRH antagonist protocol and PPOS protocol in infertile patients older than 35 years with DOR, including the comparison of the outcome of frozen embryos.

Methods

This was a retrospective cross-sectional study performed in Centre for Reproductive Medicine, First Hospital of Jilin University, Changchun, China. The data was collected from electronic medical record during January 2016 to January 2020. The study had been approved by the ethics committee of the First Hospital of Jilin University. And written informed consent was obtained from all participants.

Study population

The diagnostic criteria of DOR have not yet reached uniformity. Refer to relevant document standards, we included patients 35 and older who met any two of following criteria: $FSH \geq 10$ mIU/ mL; $AMH < 1$ ng/mL; $AFC < 7$. And our exclusion criteria were as follows: patients with severe intrauterine adhesions and endometriosis; husbands suffered azoospermia, extremely severe fromasthenospermia, oligospermia or teratozoospermia; either spouse had chromosomal diseases; polycystic ovary syndrome and other endocrine diseases.

Ovulation-stimulating regimens

For PPOS regimen, the medication would be started on the second day of the menstrual cycle if the ovarian function status was normal. Then from the day until trigger day, the patients were given hMG (Lizhu Pharmaceutical Trading Co., China) and FSH (Lizhu Pharmaceutical Trading Co., China) daily, while oral DYG (Duphaston, Abbott Biologicals B.V., The Netherlands). Transvaginal ultrasound and sex hormone tests were performed every 2–3 days to monitor follicle growth, dosage was individually

adjusted according to the monitoring results. When there were at least 1–2 follicles between 18-20mm in diameter, hCG (Ovidrel, Merck Serono S.p.A., Italy) or hCG combined with Diphereline (Ipsen Pharma Biotech, France) was used for triggering. For the antagonist regimen, the medication would be started on the second day of the menstrual cycle if the ovarian function status was normal. Then from the day until trigger day, the patients were given hMG (Lizhu Pharmaceutical Trading Co., China) and FSH (Lizhu Pharmaceutical Trading Co., China) daily. Transvaginal ultrasound and sex hormone tests were performed every 2–3 days to monitor follicle growth, dosage was individually adjusted according to the monitoring result. When the diameter of the follicle reached 14 mm, the antagonist Cetrotide (Pierre Fabre Medicament Production, Aquitaine Pharm International, France) was given to the patients. When there were at least 1–2 follicles between 18-20mm in diameter, hCG (Ovidrel, Merck Serono S.p.A., Italy) or hCG combined with Diphereline (Ipsen Pharma Biotech, France) were used for triggering.

Outcome Measures

The measured outcomes included the number of retrieved oocytes, incidence of premature LH surge, cycle cancellation rate, oocyte retrieval rate, mature oocyte rate, fertilization rate, cleavage rate, high qualified embryo rate, clinical pregnancy rate, biochemical pregnancy rate, live birth rate, miscarriage rate and ongoing pregnancy rate.

LH surge referred to the LH level was greater than 15UI/L on the day of HCG. Cycle cancellation referred to there were no viable embryos in the fresh cycles. Oocyte retrieval rate was calculated by dividing the number of retrieved oocytes by the number of follicles punctured. Mature oocyte rate was calculated by dividing the number of mature oocytes by the number of retrieved oocytes. High qualified embryo rate was the ratio of the number of high qualified embryo rate to the number of cleavage embryos at normal fertilization. Clinical pregnancy was defined as the existence of a gestational sac with or without fetal heart activity following the positive β hCG on ultrasound 4 weeks after transplantation. Biochemical pregnancy referred to the absence of a gestational sac on ultrasound although the β hCG was positive. Miscarriage meant that the gestational age was not more than 28 weeks, and the weight of the fetus was not more than 1000g. Ongoing pregnancy rate referred to absence of miscarriage after clinical pregnancy until the live birth. Live birth was defined as delivery above 28 weeks of gestational age.

Data analysis

SPSS software (Version 24.0, IBM SPSS, IBM Corp, Armonk, NY, USA) was used to analyse the data. According to distribution characteristics, continuous variables were described by mean $\pm$ SD or median (25th-75th percentile). Categorical variables were described by number (percentages). The two groups of continuous variables were compared by t-test or Wilcoxon signed rank test. The two groups of categorical variables were compared by χ^2 -test. $P < 0.05$ was considered to be significant.

Results

196 cycles were included. There were 100 cycles in the PPOS group, and 96 cycles were in the antagonist group. Table 1 shows the baseline information of two groups. There was a significant difference ($p <$

0.05) in the cancellation rate of the two groups. The cancellation rate in the PPOS group was 100.0%, and the antagonist group was 74.0%. There was also a difference ($p < 0.05$) in the distribution of fertilization methods between the two groups. ICSI accounted for 74.0% in the PPOS group, and IVF in the antagonist group accounted for 57.3%. Among the basic characteristics of the patients, except for the statistical difference ($p < 0.05$) in AFC between two groups, other characteristics showed similarity ($p > 0.05$).

Table 1
Comparison of baseline information between two groups.

Variables	PPOS group	Antagonist group	P-value
Number of cycles, n	100	96	
Cycle cancellation rate, %	100.0%(100/100)	74.0%(71/96)	< 0.001
Fertilization methods			
IVF	26(26.0%)	55(57.3%)	< 0.001
ICSI	74(74.0%)	41(42.7%)	
Age, years	39(38–43)	40.8 ± 4.1	0.544
Infertility type			
Primary	40(40.00%)	33(34.4%)	0.461
Secondary	60(60.00%)	63(65.6%)	
Infertility duration, years	4.5(2–8)	4(2–6)	0.299
BMI, kg/m ²	22.30 ± 2.84	22.26 ± 2.53	0.904
bFSH, mIU/mL	11.40(7.25–15.20)	10.30(7.81–12.51)	0.190
AMH, ng/mL	0.54 ± 0.40	0.53 ± 0.35	0.868
AFC, n	4.02 ± 1.74	5.49 ± 2.29	< 0.001

There were no significant differences ($p > 0.05$) in total dose of gonadotropins, days of stimulation, or LH on HCG administration day between two groups. Incidence of premature LH surge, oocyte retrieval rate and mature oocyte rate also showed no differences ($p > 0.05$). The total dose and total days of HMG of the PPOS group ($p < 0.05$) were higher than those of the antagonist group. For E2 and P on HCG administration day, antagonist group was higher than PPOS group ($p < 0.05$). The number of follicles with diameters greater than 20 mm on hCG day in PPOS group was lower than that in antagonist group ($p < 0.05$). The number of follicles with diameters greater than or equal to 14 mm on hCG day in PPOS group was also lower than that in antagonist group ($p < 0.05$). The number of follicles punctured and oocytes

retrieved in the antagonist group were higher than those in the PPOS group ($p < 0.05$). Results are shown in Table 2.

Table 2
Comparison of ovulation induction between two groups.

Variables	PPOS group	Antagonist group	P-value
Total dose of gonadotropins, IU	2480.25 ± 1129.19	2332.32 ± 977.13	0.329
Days of stimulation, n	10(8–12)	9.5(8–11)	0.087
Total dose of HMG, IU	1315.50 ± 779.67	1170.31 ± 784.53	0.723
Total days of HMG, n	10.00(7.00-11.75)	7.00(4.00–9.00)	< 0.001
LH on HCG administration day, IU/L	4.31(2.47–6.63)	4.07(2.16–7.12)	0.846
E ₂ on HCG administration day, pg/mL	780.25(512.03-1228.50)	1046.00(624.83-1390.25)	0.010
P on HCG administration day, IU/L	0.36(0.23–0.53)	0.58(0.34–0.96)	< 0.001
Incidence of premature LH surge, %	7.00%(7/100)	5.21%(5/96)	0.601
> 20 mm follicles on hCG administration day, n	0(0–1)	1(0–1)	< 0.001
≥ 14 mm follicles on hCG administration day, n	2(1–3)	3(2–5)	0.002
Number of follicles punctured, n	3(2–4)	4(2–6)	0.002
Number of retrieved oocytes, n	2(1–4)	3(2–5)	0.016
Oocyte retrieval rate, %	100.00% (67.00%-100.00%)	83.00% (60.75%-100.00%)	0.159
Mature oocyte rate, %	100.00% (66.67%-100.00%)	100.00% (83.93%-100.00%)	0.220

Table 3 shows the laboratory indicators of PPOS group and antagonist group. There were no significant differences ($p > 0.05$) in fertilization rate, cleavage rate, or high qualified embryo rate between two groups.

Table 3
Comparison of laboratory indicators between two groups.

Variables	PPOS group	Antagonist group	P-value
Fertilization rate, %	100.00%(50.00%-100.00%)	100.00%(72.00%-100.00%)	0.282
Cleavage rate, %	100.00%(87.50%-100.00%)	100.00%(70.00%-100.00%)	0.852
High qualified embryo rate, %	0.00%(0.00%-66.67%)	33.33%(0.00%-50.00%)	0.327

57 cycles entered FET cycle in PPOS group and 44 cycles in antagonist group. There was no significant difference between two groups of FET outcome indicators ($p > 0.05$). (See Table 4.)

Table 4
Comparison of FET outcomes between two groups.

Variables	PPOS group	Antagonist group	P-value
Clinical pregnancy rate, %	28.10%(16/57)	29.50%(13/44)	0.871
Biochemical pregnancy rate, %	5.30%(3/57)	2.30%(1/44)	0.803
Live birth rate, %	14.00%(8/57)	20.50%(9/44)	0.393
Miscarriage rate, %	25.00%(4/16)	23.10%(3/13)	1.000
Ongoing pregnancy rate, %	18.80%(3/16)	7.70%(1/13)	0.606

Discussion

To our knowledge, there were few studies comparing the effects of the two regimens for elderly patients with DOR. In this study, our research subjects were women over the age of 35 with DOR undergoing IVF treatment. In terms of the effect of inhibiting the premature LH surge, PPOS regimen and antagonist regimen showed no difference. Although the final outcome of the frozen embryo transfer cycles of two regimens showed similarities, the antagonist regimen was better than the PPOS regimen in terms of ovulation induction outcome.

DOR is a difficult problem in the treatment of fertility. Because DOR patients do not respond well to ovarian stimulation, COS becomes a particularly critical step in ART cycles [14]. We selected the two most clinically used ovulation stimulation regimens to compare which regimen used by DOR patients would have better oocyte-obtained outcome and fertility outcome. Patients with DOR were more likely to experience premature LH surge [12]. One of the advantages of the PPOS regimen is that it can prevent premature LH surge [10]. Therefore, we first compared its effect with the antagonist regimen in suppressing premature LH surge. We found there was no difference which was different from other studies. In a study of patients with endometriosis, the LH level on trigger day of PPOS group patients was lower than that in the antagonist group [15]. Chen et al. proved that compared with the antagonist

regimen, PPOS regimen could better prevent the appearance of premature LH surge for poor responders [16]. But we found similar conclusion in a study [17] that also targeted DOR patients. There was also no difference in the incidence of premature LH surge between the flexible PPOS group and antagonist group. Subsequently, the researcher also conducted subgroup analyses based on the AMH value and AFC, and no difference was found. Therefore, for patients with DOR, there was no difference in the effectiveness of the two regimens for pituitary suppression.

From the process of ovulation induction and the number of retrieved oocytes, the antagonist program may be more suitable for DOR patients over 35 years old. The proliferation and differentiation of endometrial cells depend on estrogen and progesterone. Levels of estradiol and progesterone play a key role in the preparation of the uterus before implantation [18]. There is still controversy as to whether estradiol and progesterone levels on trigger day are associated with IVF outcomes [18, 19]. Although the estradiol and progesterone levels on HCG administration days in the antagonist group were higher than those in the PPOS group in this study, the pregnancy outcome did not show any difference. Related studies [18] proved that the effect of serum estradiol on IVF pregnancy outcome might be related to concentration, and it was believed that the optimal concentration range for positive outcomes in patients over 38 years old is 2000–3000 pg/mL, and the range is higher for patients younger than 38 years old. A meta-analysis with a sample size of 55,000 [20] showed that there was a negative correlation between progesterone levels and pregnancy rate, and a decrease in pregnancy rate would be seen when the progesterone level reached the range of 0.8–1.1 ng/ml. In this study, the two groups of trigger-day estradiol levels did not reach 2000 pg/ml, and the progesterone levels did not reach 0.8ng/ml. Therefore, we could only provide a reference that estradiol and progesterone levels on HCG administration day might be higher in patients with DOR from antagonist regimen than PPOS regimen.

In terms of retrieved oocytes results, the antagonist regimen was better than the PPOS regimen. No difference in the number of oocytes retrieved was observed between PPOS regimen and antagonist regimen in patients with low ovarian response or polycystic ovary syndrome (PCOS) [16, 21]. In a study comparing the PPOS regimen with the long regimen in DOR patients over 35 years of age, no difference was found in the number of oocytes retrieved either [22]. However, in this study, the number of follicles in different stages and the number of retrieved oocytes of the antagonist group were all higher than those of the PPOS group. Although the final clinical outcomes of the two groups were not statistically different, the key to promoting ovulation in patients with DOR is to reduce the rate of early ovulation and maximize the possibility of retrieving oocytes. And the older the patients get, the easier it is to ovulate prematurely [12]. Therefore, from the perspective of oocytes retrieving, in terms of the results of this study, the antagonist regimen might be more suitable for DOR patients over 35 years of age who received IVF-assisted pregnancy.

There were some limitations in our study. Firstly, this was a retrospective study, which proved that the purpose of the study was not as strong as a randomized controlled study. What's more, the number of patients collected during the study period was relatively small. A larger sample size is needed for further research in the future. Since the embryos of patients using PPOS regimen were all frozen, we couldn't

compare the outcome of the fresh cycle of two regimens. So we compared their frozen embryo clinical outcomes. This was also a feature of this study.

Conclusions

In conclusion, for DOR patients over 35 years of age, antagonist regimen would retrieve more oocytes than PPOS regimen. Patients using the antagonist regimen would also have higher levels of estradiol and progesterone on the trigger day than in the PPOS group. There was no difference in the final pregnancy outcome between two groups. Therefore, from the perspective of oocyte retrieving, the antagonist regimen might be more suitable for DOR patients over 35 years old. Of course, the conclusions will need to be verified by a larger sample size and more rigorous research design in the future.

List Of Abbreviations

PPOS

progestin-primed ovarian stimulation

DOR

diminished ovarian reserve

IVF

in vitro fertilization

FET

frozen embryo transfer

ART

assisted reproductive technology

ACOG

American Association for Obstetrics and Gynecology

COS

Controlled ovarian stimulation

LH

luteinizing hormone

OHSS

hyperstimulation syndrome

GnRH

Gonadotrophin-releasing hormone

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the First Hospital of Jilin University (2021-486). Written informed consent was

obtained from each participant included in the study.

Consent for publication

Not applicable.

Availability of data and material

The data used in this study is not available for public view, but available from the corresponding author upon reasonable request.

Competing interests

All authors declare that they have no conflicts of interest.

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Authors' contributions

MHW, RZL, RXW and QX designed and performed the study. MHW, RXW and QX analyzed the data. MHW and RXW drafted the manuscript. MHW, QX, YTJ and HGZ participated in revising the draft of the manuscript. All authors approved the final version of the paper for submission.

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