Original Article

Efficacy of progestin-primed ovarian stimulation (PPOS) versus minimal stimulation in women of advanced maternal age with poor ovarian response under the Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) criteria

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Background: We investigated the efficacy of progestin-primed ovarian stimulation (PPOS) and minimal stimulation using clomiphene citrate (CC) + gonadotropin (Gn) for *in-vitro* fertilization-embryo transfer (IVF-ET) in advanced maternal age (AMA) women with poor ovarian response (POR) according to the Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) criteria.

Methods: A retrospective analysis was performed using the data of AMA patients who had received IVF-ET due to a low ovarian reserve. The enrolled patients were screened according to the POSEIDON group 4 criteria. 102 patients were included in the study, including 52 in the PPOS group and 50 in the minimal stimulation group (who received CC + Gn). The duration of Gn administration, Gn dose, estradiol (E2), and luteinizing hormone (LH) levels on the day of trigger, the cancellation rate of the oocyte retrieval cycle, the number of oocytes retrieved, the number of metaphase II (MII) oocytes, and IVF laboratory outcomes during ovarian stimulation were compared between the 2 groups.

Results: No significant differences were found in terms of age, infertility, body mass index (BMI), and basal follicle-stimulating hormone, LH, E2, AFC, and AMH between the 2 groups (all P>0.05). The duration of ovarian stimulation [(9.43±2.44) *vs.* (7.48±3.09) days, P<0.05] was significantly longer and the total Gn dose [(2,423.22±738.66) *vs.* (1,579.68±728.86) IU, P<0.05] were significantly higher in the PPOS group than the minimal stimulation group. The LH value on the day of trigger in the PPOS group (3.28 mIU/mL) was significantly lower than that in the minimal stimulation group (5.57 mIU/mL) (P<0.05). The number of oocytes retrieved, normal fertilization rate, number of good-quality embryos on day 3, number of transferable embryos, and number of frozen blastocysts did not differ significantly between the 2 groups (all P>0.05). The proportion of MII oocytes was significantly higher in the PPOS group than the minimal stimulation group (94.05% *vs.* 81.40%, P<0.05).

Conclusions: For patients in the POSEIDON group 4, PPOS effectively blocked the premature LH surge and increased the proportion of mature oocytes. Thus, it is a feasible ovulation stimulation protocol for AMA women with POR.

Keywords: Patient-oriented Strategies Encompassing IndividualizeD Oocyte Number criteria (POSEIDON criteria); poor ovarian response; advanced maternal age (AMA); progestin-primed ovarian stimulation (PPOS); minimal stimulation

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Introduction

With the implementation of the "2-child" and "3-child" policies in China, an increasing number of women of advanced maternal age (AMA) have a desire to give birth. However, many AMA women face a number of problems, such as a decreased ovarian reserve and poor oocyte quality, which seriously affect the clinical pregnancy rate. At present, many AMA women choose to use assisted reproductive technology (ART) for which the selection of a proper ovarian stimulation regimen is particularly important (1).

AMA women with a poor ovarian response (POR) who underwent in-vitro fertilization-embryo transfer (IVF-ET) at our center and met the criteria of Patient-Oriented Strategies Encompassing Individualized Oocyte Number (POSEIDON) group 4 (2) were enrolled in the current study. We retrospectively compared the laboratory and clinical outcomes of patients who had received progestin-primed ovarian stimulation (PPOS) to those of patients who had received minimal stimulation using clomiphene citrate (CC) + gonadotropin (Gn) to gather evidence on the selection of ovarian stimulation regimens for IVF-ET in AMA women in POSEIDON group 4. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1448/rc).

Highlight box

Key findings

- PPOS is a safe and effective ovulation stimulation option for IVF-ET in AMA women with POR under the POSEIDON criteria.

What is known and what is new?

- Many women of advanced age in China have pregnancies with assisted reproductive technology.
- The article compares two commonly used ovulation promotion protocols.

What is the implication, and what should change now?

- PPOS is worth promoting in the future. For patients in POSEIDON group 4, PPOS was more effective than the minimal stimulation in blocking the premature LH surge and increasing the proportion of mature oocytes. Therefore, it is a viable ovulation promotion option for AMA women with POR. In the future, we intend to increase our sample sizes and perform prospective randomized controlled studies to further explore the efficiency and safety of the PPOS protocols.

Methods

Subjects and grouping

The data of 102 patients who had received ovarian stimulation for IVF-ET at the Department of Reproductive Medicine of The Fourth Hospital of Hebei Medical University, between November 1, 2020 and November 1, 2021 were retrospectively analyzed. The PPOS group comprised 52 patients and the minimal stimulation group (which received CC + Gn) comprised 50 patients. All the patients met the following POSEIDON group 4 criteria: (I) were aged ≥35 years; (II) had a decreased ovarian reserve; (III) had serum anti-Mullerian hormone (AMH) <1.2 ng/mL; and (IV) had an antral follicle count (AFC) <5 (2). According to the Poseidon criteria women aged 35 years or older are defined as advanced maternal age (2). The clinical and laboratory data of the enrolled patients were downloaded from the ART management system software database of The Fourth Hospital of Hebei Medical University. Based on the ovarian stimulation regimens, these subjects were divided into the PPOS group and the minimal stimulation group. The study was approved by the ethics committee of The Fourth Hospital of Hebei Medical University (No. 2021KS010). Individual consent for this retrospective analysis was waived. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Ovarian stimulation protocols

All the patients underwent reproductive-endocrine tests (electrochemiluminescence immunoassays) and transvaginal ultrasound on the 2nd to 4th days of their menstrual cycles. Ovarian stimulation was initiated in patients who met the following criteria: (I) had no cysts either ovary; (II) had at least 1 visible basal follicle; and (III) had follicles that were all sized <10 mm. If a patient did not meet these criteria, the ovarian stimulation cycle was canceled.

Minimal stimulation

CC (50 mg, Codal Synto Ltd, Shanghai, China) was orally administered from the 2nd to 3rd day of the menstrual cycle to the trigger day. An intramuscular injection of urofollitropin [150–225 IU/d, urofollitropin-follicle stimulating hormone (u-FSH), Lishenbao, 75 IU/vial, Livzon, Zhuhai, China] was also administered according to follicle count and hormone levels. The time of trigger and trigger medications were as follows: when there was 1

or more follicles ≥20 mm in diameter or 3 or more follicles ≥18 mm in diameter, the oocytes were retrieved 34–36 hours after the simultaneous injection of 0.2 mg of short-acting GnRH-a (Diphereline, Ferring, Germany) and 2,000 IU of human chorionic gonadotophin (HCG) (1,000 IU/vial; Livzon, Zhuhai, China).

PPOS

Medroxyprogesterone acetate (MPA; 10 mg/d, Xianju Pharma, Zhejiang, China) was orally administered from the 2nd–3rd day of the menstrual cycle to the trigger day. An intramuscular injection of urofollitropin (225 IU/d, u-FSH, Lishenbao, 75 IU/vial, Livzon, Zhuhai, China) was also administered according to the follicle count and hormone levels. The time of trigger and trigger medications were as follows: when there was 1 or more follicles ≥20 mm in diameter or 3 or more follicles ≥18 mm in diameter, the oocytes were retrieved 34–36 hours after the simultaneous injection of 0.2 mg of short-acting GnRH-a (Diphereline, Ferring, Germany) and 2,000 IU of HCG (1,000 IU/vial; Livzon, Zhuhai, China).

IVF

IVF was routinely performed. Semen was collected from the male partner when the oocytes were retrieved from the woman. After the semen was fully liquefied, gradient sperm separation was performed on the SpermGrad™, and the sperm concentration was adjusted to 10×10^6/mL. The sperm was added 3–4 hours after oocyte retrieval, and the fertilization was observed at 16–20 hours. Embryo development was observed at 72 hours, and embryo quality was assessed using the following criteria (3): grade A: even-sized blastomeres, clear and homogeneous cytoplasm without vacuoles, and <10% fragmentation; grade B: slightly different sized blastomeres, clear cytoplasm with small vacuoles, and 6–20% fragmentation; grade C: remarkably different sized blastomeres, rough cytoplasm with large vacuoles, and 21–50% fragmentation; and grade D: seriously different sized blastomeres, cytoplasm with serious vacuolization; ≥50% fragmentation. If there were abnormal zona pellucida, cytosolic vacuoles, large perivitelline space, perivitelline space granularity, and scattered blastomeres, the grade would be lowered by 1 grade.

The criteria for usable embryos were as follows: the number of blastomeres ≥4 on day 3 and the embryo was graded as grade C or above (3). The criteria for good-quality embryos were as follows: the embryos were at 7–9 cells by 72 hours after egg retrieval; the blastomeres were evenly or slightly unevenly sized; the blastomeres were not multinucleated; and the fragmentation rate was ≤20%. The blastocyst consists of a cavity, inner cell mass, and trophoblasts. The blastocysts were graded using the Gardner system, under which grades 4AA, 4BB, 4AB, and 4BA indicate good-quality blastocysts, and grade 4CC blastocysts are not cryopreserved. Blastocyst cultures were performed in both groups, and a freeze-only strategy was applied to the cultured blastocysts.

Main measures

The demographic data, duration of Gn administration, dose of Gn, levels of E2, and luteinizing hormone (LH) on the day of HCG administration, cancellation rate of egg retrieval cycle, number of oocytes retrieved, number of 2-pronuclei (2PN) zygotes, proportion of metaphase II (MII) oocytes, fertilization rate, number of transferable embryos, number of cryopreserved blastocysts, proportion of good-quality embryos on day 3, and blastocyst formation rate were compared between the 2 groups (all $P>0.05$). According to the Vienna consensus on the ART laboratory performance indicators (4), the following formulae were applied for the specific indicators: proportion of MII oocytes = number of MII oocytes/number of oocytes retrieved × 100%; fertilization rate = number of oocytes fertilized/number of oocytes retrieved × 100%; proportion of good-quality embryos on day 3 = number of good-quality embryos on day 3/number of normal cleavage-stage embryos × 100%; and blastocyst formation rate = number of blastocysts formed/total number of cleavage-stage embryos undergoing blastocyst culture × 100%.

Statistical analysis

The statistical analysis was performed using the SPSS 26.0 software package. The measurement data were compared using the 2-sample *t*-test. The normally distributed measurement data are expressed as the mean ± standard deviation ($\bar{x}\pm$SD). The non-normally distributed measurement data were analyzed using the Mann-Whitney U test, in which the medians were used for the comparisons, and the data are presented as the medians (25th percentile, 75th percentile) [M (P25, P75)]. The count data are presented as the rate (%) and were analyzed using the χ^2

Table 1 Comparison of the general data between the 2 groups [M (P25, P75)]

Group patients [n]	Age (years)	Years of infertility (years)	BMI (kg/m^2)	Basal FSH (mIU/mL)	Basal E2 (pg/mL)	Basal LH (mIU/mL)	AMH (ng/mL)	AFC (n)
PPOS group [52]	40.50 (38.00, 43.00)	3.00 (1.00, 6.00)	24.00 (22.43, 25.60)	11.91 (8.14, 14.15)	42.78 (26.76, 52.87)	3.90 (3.53, 5.60)	0.36 (0.13, 0.56)	2.00 (1.00, 4.00)
Minimal stimulation group [50]	39.00 (37.00, 42.00)	4.00 (2.50, 8.00)	23.40 (21.85, 26.00)	11.35 (7.53, 14.92)	42.77 (21.58, 60.85)	3.91 (3.38, 4.92)	0.37 (0.12, 0.52)	2.00 (2.00, 4.00)
z value	–1.058	–1.940	–0.802	–0.545	–0.259	–0.624	–0.117	–0.715
P value	0.290	0.052	0.422	0.586	0.796	0.624	0.906	0.715

The data are presented as the medians (25th percentile, 75th percentile). BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; AMH, anti-Mullerian hormone; AFC, antral follicle count; PPOS, progestin-primed ovarian stimulation.

Table 2 Comparison of the clinical ovulation stimulation indicators between the 2 groups [($\bar{x}$±SD), M (P25, P75), %]

Group patients [n]	Duration of Gn use (days)	Total Gn dose (IU)	E2 level on trigger day (pg/mL)	LH level on trigger day (mIU/mL)	Cancellation rate of oocyte retrieval cycle (%)
PPOS group [52]	9.43±2.44*	2,423.22±738.66*	827.75 (286.15, 1234.50)	3.28* (2.10, 4.91)	0 (0/50)
Minimal stimulation group [50]	7.48±3.09	1,579.68±728.86	843.00 (530.60, 1,132.00)	5.57 (4.42, 8.03)	6 (3/50)
$t/z/\chi^2$ value	3.341	5.438	–0.750	–4.758	3.093
P value	0.001*	0.000*	0.453	0.000*	0.242

*, P<0.05, compared to the minimal stimulation group. SD, standard deviation; Gn, gonadotropin; LH, luteinizing hormone; PPOS, progestin-primed ovarian stimulation.

test or Fisher's exact test. A P value of <0.05 was considered statistically significant.

Results

General data

A total of 102 patients were enrolled in the study. There were no significant differences between the 2 groups in terms of age, infertility years, body mass index (BMI), and baseline FSH, LH, E2, AFC, and AMH levels (all P>0.05), suggesting that the 2 groups were comparable (*Table 1*).

Ovarian stimulation indicators

The PPOS group had significantly longer duration of Gn administration [(9.43±2.44) *vs.* (7.48±3.09) days] and a higher Gn dose [(2,423.22±738.66) *vs.* (1,579.68± 728.86) IU] than the minimal stimulation group (both P<0.05). However, the LH value on the day of trigger in the PPOS group (3.28 mIU/mL) was significantly lower than that in the minimal stimulation group (5.57 mIU/mL) (P<0.05). The cancellation rate of egg retrieval cycle was lower in the PPOS group than the minimal stimulation group, but the difference was not statistically significant (P>0.05) (*Table 2*).

Laboratory data

The proportion of MII oocytes was significantly higher in the PPOS group than the minimal stimulation group (94.05% *vs.* 81.40%, P<0.05). The number of oocytes retrieved, number of 2PN zygotes, fertilization rate, proportion of good-quality embryos on day 3, number of transferable embryos, number of cryopreserved blastocysts, and blastocyst formation rate did not differ significantly between these 2 groups (all P>0.05) (*Table 3*).

Discussion

With the rapid socioeconomic development and the

Table 3 Comparison of the laboratory data between the 2 groups [($\bar{x}$±s), %]

Group patients [n]	Number of retrieved oocytes (n)	Number of 2PN zygotes (n)	Number of transferable embryos (n)	Number of cryopreserved embryos (n)	Proportion of MII mature oocytes (%)	Fertilization rate (%)	Proportion of high-grade embryos on day 3 (%)	Blastocyst formation rate (%)
PPOS group [52]	1.73±1.24	1.68±0.95	1.45±1.23	1.40±0.95	94.05 (79/84)*	70.24 (59/84)	46.94 (23/49)	72.00 (36/50)
Minimal stimulation group [50]	1.75±1.26	1.42±0.49	1.38±0.50	1.37±1.11	81.40 (70/86)	67.44 (58/86)	39.02 (16/41)	62.22 (28/45)
t value/χ^2 value	0.738	–0.089	0.118	1.274	6.283	0.155	0.569	1.030
P value	0.462	0.930	0.906	0.211	0.012*	0.694	0.450	0.310

*, P<0.05, compared to the minimal stimulation group. 2PN, 2-pronuclei; MII, Metaphase II; PPOS, progestin-primed ovarian stimulation.

adoption of 2- and 3-child policies in China, more women of AMA have a desire to become pregnant. It is well known that age is an important factor affecting a woman's chance to conceive. Women who are aged >35 years and have failed to get pregnant after 6 (or less) months of trying should seek active assessment and treatment. While patients aged >40 years of age should be assessed and treated immediately (1). During IVF cycles, AMA women often have POR, which is characterized by a failure to respond adequately to an ovarian hyperstimulation protocol or to recruit enough follicles, resulting in a reduction in the number of oocytes retrieved, an increased cycle cancellation rate, and a low clinical pregnancy rate (5). However, the mechanism of POR remains unclear, and the clinical management of POR patients, and the choice of the ovarian stimulation protocol remains controversial.

In 2011, the European Society of Human Reproduction and Embryology (ESHRE) proposed the Bologna criteria for the definition of POR (6). However, the criteria has been controversial, as it does not take into account factors related to a successful AST (e.g., aneuploidy rates in embryos from AMA women and different ovarian responses to Gn stimulation), and it does not provide recommendations for the clinical management of POR (7).

The POSEIDON stratification criteria (2) were released in 2016, and divide POR women into the following 4 groups: POSEIDON group 1 (women aged <35 years, with an AMH ≥1.2 ng/mL, and AFC ≥5); POSEIDON group 2 (women aged ≥35 years, with an AMH ≥1.2 ng/mL, and AFC ≥5); POSEIDON group 3 (women aged <5 years, with an AMH <1.2 ng/mL, and AFC <5); POSEIDON group 4 (women aged ≥35 years, with an AMH <1.2 ng/mL, and AFC <5). Groups 1 and 2 comprise patients with unexpected POR due to abnormal ovarian Gn response, while groups 3 and 4 comprise POR patients with a low ovarian reserve. It is better to select individualized ovulation induction regimens for different types of POR patients (8).

In the IVF-ET cycle, the commonly used ovarian stimulation strategies (e.g., natural cycle and minimal stimulation) in AMA women cannot address the early LH surge due to the defective production of the gonadotrophin surge-attenuating factor in POR patients (9). As a result, problems such as follicular dysplasia, poor egg quality, and a high cycle cancellation rate often occur in the superovulation cycles.

MPA is an effective oral alternative for preventing premature LH surges in women undergoing controlled ovarian hyperstimulation for *in-vitro* fertilization. Kuang *et al.* (10) were the first to propose the PPOS protocol, in which MPA and human menopausal gonadotropin (hMG) are administered simultaneously for ovarian stimulation to induce a high progesterone status and thus enable LH suppression to persist. This strategy effectively prevents a premature LH surge and reduces premature ovulation during hyperovulation.

The new ovarian stimulation regimen, PPOS, has gained increasing use, and a number of clinical studies have demonstrated its value for POR patients. PPOS has been widely applied in clinical, a recent meta-analysis showed that PPOS reduces the need for cycle cancellation, increases the quality of follicles and embryos, improves the pregnancy rate, and thus presents an effective option for IVF-ET in patients with POR (11). In a clinical study of 117 aged women with POR, Mu *et al.* (12) also found that the number of follicles, the number of eggs, clinical pregnancy, and live birth rates in the PPOS group were significantly superior to those in the ultrashort protocol group. Huang *et al.* (13) found that the application of MPA to the PPOS regimen

did not affect neonatal outcomes or increase the risk of congenital malformations compared to the conventional GnRH-agonist short protocol. Thus, PPOS is an effective, safe, and reliable ovarian stimulation regimen for AMA patients with POR.

In our current study, the values of PPOS and minimal stimulation regimens in the IVF cycles of AMA patients with POR were compared, and we found that the Gn dose and the duration of Gn use were significantly higher and longer in the PPOS group than the minimal stimulation group, and these were the disadvantage of PPOS compared to the minimal stimulation protocol. Similarly, Peng *et al.* (14) assumed that such differences might be explained by the fact that CC itself has an ovulation stimulation effect, and patients need to add less exogenous Gn during hyperovulation.

The minimal stimulation protocol has the advantages of a short Gn time and low dosage; however, its disadvantages are also obvious for AMA patients with POR; for example, it has a high incidence of a premature LH surge, premature ovulation, and high cycle cancellation rate (15). In the current study, the LH level on the day of trigger was significantly lower in the PPOS group than the minimal stimulation group. The IVF cycle was canceled due to premature ovulation in 3 patients in the minimal stimulation group, but no such cycle cancellation occurred in the PPOS group. The difference was not statistically significant; however, the results suggested that PPOS lowered the LH level on the day of trigger and reduced the cycle cancellation rate, which is consistent with the findings of previous studies (16,17).

The proportion of MII mature oocytes was significantly higher in the PPOS group than the minimal stimulation groups. Conversely, the differences in the number of retrieved oocytes, number of 2PN zygotes, number of transferable embryos, number of cryopreserved embryos, fertilization rate, proportion of high-grade embryos on day 3, and blastocyst formation rate did not differ significantly between the 2 groups. It may be that in patients treated with the PPOS protocol, progesterone use inhibits the positive feedback effect of estrogen on the hypothalamic-pituitary-ovarian axis, leading to the decreased secretion of both pituitary Gns and LH, which in turn prevents the early occurrence of spontaneous ovulation or premature luteinization of follicles without affecting egg quality (18).

Our current study was limited by its retrospective and non-randomized design and small sample size. Given the persistently high progesterone status in the follicular phase, the effect of CC on endometrial receptivity, and the requirement of AMA women with POR on embryo accumulation, we did not include patients who were in the fresh embryo transfer cycle, and thus we did not compare the clinical pregnancy and miscarriage rates after implantation. Some studies have shown that PPOS also could be applied for young women with poor ovarian response (19,20), however, this group of individuals was not included in our research due to the scope of the study. In the future, we intend to increase our sample sizes and perform prospective randomized controlled studies to further explore the efficiency and safety of the PPOS protocols.

In summary, the PPOS protocol can effectively inhibit premature LH surge, prevent premature ovulation, reduce the cancellation rate of oocyte retrieval cycle, and improve oocyte maturation in AMA patients with POR. Thus, PPOS is a safe and effective ovulation stimulation option for IVF-ET in AMA women with POR under the POSEIDON criteria.

Conclusions

PPOS has been widely applied in clinical, for patients in the POSEIDON group 4, PPOS effectively blocked the premature LH surge and increased the proportion of mature oocytes. Thus, it is a feasible ovulation stimulation protocol for AMA women with POR. In the future, we intend to further retrospectively analyze the post-embryo transfer outcomes obtained with both regimens and increase the sample size and conduct a prospective randomized controlled study to continue exploring the efficiency and safety of the PPOS.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1448/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-1448/dss

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-1448/coif). Both authors have no conflicts of interest to declare.

Ethical Statement: Both authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of The Fourth Hospital of Hebei Medical University (No. 2021KS010). Individual consent for this retrospective analysis was waived.

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