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ORIGINAL RESEARCH

Effect of Elevated Progesterone Levels on hCG Trigger Day on Clinical Pregnancy Outcome in Short-Acting GnRHa Downregulated Cycles

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Background: Previous studies suggested higher serum progesterone (P) levels were strongly associated with a lower clinical pregnancy rate (CPR) for in vitro fertilization-embryo transfer (IVF-ET). However, the effect of increased serum P levels on the day of human chorionic gonadotropin (hCG) administration on clinical outcomes in short-acting gonadotropin-releasing hormone agonist (GnRHa) downregulated IVF-ET cycles remains unclear.

Methods: We conducted a retrospective cohort study from January 2017 to December 2021, which included a total of 1664 patients receiving their first short-acting GnRHa IVF-ET cycles at our reproductive medicine centre of Nanjing Drum Tower Hospital. The smooth curve fitting and interaction analysis were employed to analyse the association between the CPR and the serum P levels with different embryo types (cleavage-stage embryo or blastocyst). In addition, total cycles were grouped according to different P levels on the trigger day of hCG administration for further analysis.

Results: The CPR of patients with increased serum P level (higher than 1.5 ng/mL) on the hCG day did not decrease. A smoothing curve fitting showed that the CPR did not change obviously with the increase in serum P levels. Subgroup analysis of different types of embryos transferred showed that no correlation was observed between the CPR and serum P levels on the day of hCG administration in cleavage-stage embryo transfer cycles. However, the CPR of patients receiving blastocyst transfer showed a downward trend with the increase in serum P levels. At the same time, an interaction analysis also confirmed that the CPR of blastocyst transfer was more likely to be affected by elevated serum P levels on the hCG day.

Conclusion: In the luteal phase short-acting GnRHa downregulated IVF-ET cycles, the elevated serum P levels on the hCG day did not affect the CPR of cleavage-stage embryo transfer but reduced the CPR of blastocyst transfer.

Keywords: short-acting GnRHa, elevated progesterone level, hCG trigger day, clinical pregnancy rate, blastocyst transfer

Background

Oestrogen and progesterone levels jointly regulate the synchronous development and receptivity of endometrium.[1,2] Progesterone (P) is an important factor to promote the transformation of endometrium to secretory phase, while the early increase of the P level on the hCG trigger day in controlled ovarian hyperstimulation (COH) cycles will adversely affect the transformation of endometrium and endometrial receptivity and inhibit embryo implantation.[3–8] Most previous studies suggested that elevated P levels would have a negative impact on the clinical outcome of in vitro fertilization/intracytoplasmic sperm injection and embryo transfer (IVF/ICSI-ET) cycles.[7,9–12] However, there are also several studies

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suggesting that it has no adverse effect on the clinical outcome of IVF/ICSI cycles.[13–15] Therefore, the influence of serum P levels on the hCG day on clinical outcome remains controversial.

Previous studies suggested that the increase in serum P level (>1.5 ng/mL) on the day of hCG administration was related to the significant decrease in the persistent pregnancy rate after the assisted reproductive technology (ART) cycle.[16] The increase of serum P level on the hCG day occurred in about 6–30% COH cycles. Papanikolaou et al[17] revealed that when the cleavage-stage embryos were transferred, the increased P (>1.5 ng/mL) had a significant negative impact on the pregnancy outcome. However, no negative effects on blastocyst transfer were observed, suggesting that the selection of blastocyst transfer may overcome the adverse effects of elevated P levels. On the contrary, in our recent study, we found that the increase in serum P levels on the hCG day in long-acting GnRHa downregulated IVF-ET cycles had adverse effects on blastocyst transfer. To explore whether the same phenomenon exists in patients who receive short-acting GnRHa downregulated IVF-ET cycles, we have conducted a retrospective study at our reproductive medicine centre from 2017 to 2021. We further explored whether the increase of P levels on the hCG day had different effects on the clinical outcomes of different types of embryos (cleavage-stage embryo or blastocyst) transfer.

Methods

Study Population

Our retrospective cohort study was focused on patients undergoing their first short-acting GnRHa IVF-ET cycles. All enrolled participants received the ART treatment from 2017 to 2021 at our reproductive medicine centre of Nanjing Drum Tower Hospital. Each couple was informed of the possibility of using their basic information and treatment data during the IVF cycle for subsequent study. The study approval was obtained from Nanjing Drum Tower Hospital ethics committee, and patients were provided written informed consent. The exclusion criteria were as follows: (1) over 45 years old; (2) intracytoplasmic sperm injection (ICSI) cycles; (3) combined hydrosalpinx or lesions of the uterine cavity, such as endometrial polyps and endometrial dysplasia; (4) adenomyosis or endometriosis. 1664 IVF-ET cycles were enrolled in this study.

Luteal Phase Short-Acting GnRHa Long Protocol for Controlled Ovarian Stimulation

A short-acting GnRHa (triptorelin acetate, decapeptyl, Ferring GmbH, 0.1 mg) was administered in 5 to 7 days after ovulation. The patients received GnRHa injection every day for 14 days (0.1 mg i.h. q.d. for 10 days and 0.05 mg i.h. q.d. for 4 days). The levels of sex hormone, such as oestradiol (E_2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and P, and the diameter and number of follicles were measured after GnRHa downregulation. After meeting the criteria of pituitary downregulation, recombinant FSH (rFSH, Gonal-F, Merck Sereno, 75–300 IU i.h.) was injected according to the female age, body mass index (BMI), basal FSH level, and antral follicle count (AFC). Recombinant LH (rLH, Luveris, Merck Sereno, 75–150 IU i.h.) or human menopausal gonadotropin (HMG, Menotropins for Injection, Livzon Pharm, 75–300 IU i.m.) was added or not. The dosage of gonadotropin (Gn) was adjusted based on follicular growth rate and serum hormone (FSH, LH, E_2, P) levels. Recombinant hCG (rhCG, Merck Sereno, 250 μg, i.h.) or hCG (Chorionic Gonadotropin for Injection, Livzon Pharm, 10,000 IU, i.m.) was injected to trigger ovulation as 1–2 dominant follicles reached 18 mm. The oocytes were collected 36–38 hours after triggering. Mature oocytes (metaphase II, MII) were fertilization and cultured to different embryo stages (cleavage-stage embryos or blastocysts). The whole embryo freezing scheme was conducted for the increased serum P level (>2.5 ng/mL) on the trigger day.

Embryo Transfer and Pregnancy Detection

The abdominal ultrasound-guided fresh embryos transfer was conducted for patients without abnormal conditions. The cleavage-stage embryos were transferred on the 3rd day and blastocysts were transferred on the 5th day after oocyte retrieval. Serum β-human chorionic gonadotropin (β-hCG) levels were detected 12–14 days after embryo transfer to determine biochemical pregnancy. Ultrasound examination was performed 28–30 days after embryo transfer in patients with positive β-hCG results to confirm the clinical pregnancy, which was defined as the presence of a gestational sac. Luteal support was maintained for 55–60 days after embryo transfer of pregnant patients. The patients were continuously

followed up to assess any abnormalities in pregnancy and until live birth. The patients were continuously followed up until the birth of the newborn to evaluate the abnormal conditions of persistent pregnancy and live birth.

Statistical Analysis

To analyse the association between serum P levels on the hCG day and the CPR in short-acting GnRHa downregulated IVF-ET cycles, a smooth curve fit analysis was conducted. According to the reported cut-off value of P levels (1.5 ng/mL), all cycles were divided into two groups (Group A: $P \leq 1.5$ ng/mL; Group B: $P > 1.5$ ng/mL). Propensity score matching was conducted for the lower number of patients in Group B. According to different types of transferred embryos, further subgroup analysis was carried out, and then, an interaction analysis was taken to confirm the influence of embryo stages on the association between P levels and CPR. All variables are presented as the mean ± standard deviation (SD). $P < 0.05$ was considered statistically significant. Our analyses were performed with R software version 3.6.0 (http://www.R-project.org) and EmpowerStats software (www.empowerstats.com, X&Y solutions, Inc. Boston MA).

Results

Relationship Between Serum P Levels on the hCG Day and the CPR

A smooth curve fitting revealed that the CPR did not change as the serum P level on the hCG day increased (Figure 1). All data were divided into two groups: Group A, P levels less than or equal to 1.5 ng/mL, and Group B, P levels greater than 1.5 ng/mL (Table 1). The female age, BMI, basal FSH levels, AFC, duration of infertility and Gn stimulation duration were similar in these two groups. But total dose of Gn was greater in Group A. The serum P level on the trigger day was significantly higher in Group B than that in Group A (1.78 ± 0.22 vs 0.60 ± 0.33 ng/mL). The number of oocytes retrieved was significantly higher in Group B, while the number of available embryos showed no difference in these two groups. There were no difference in the clinical outcomes (CPR, early miscarriage rate or live birth rate) between Group A and B. Because the number of patients in Group B was too small, the propensity score matching was employed to control confounding variables. Similarly, the CPR, early miscarriage rate and live birth rate were similar between the two groups after propensity score matching (Table S1).

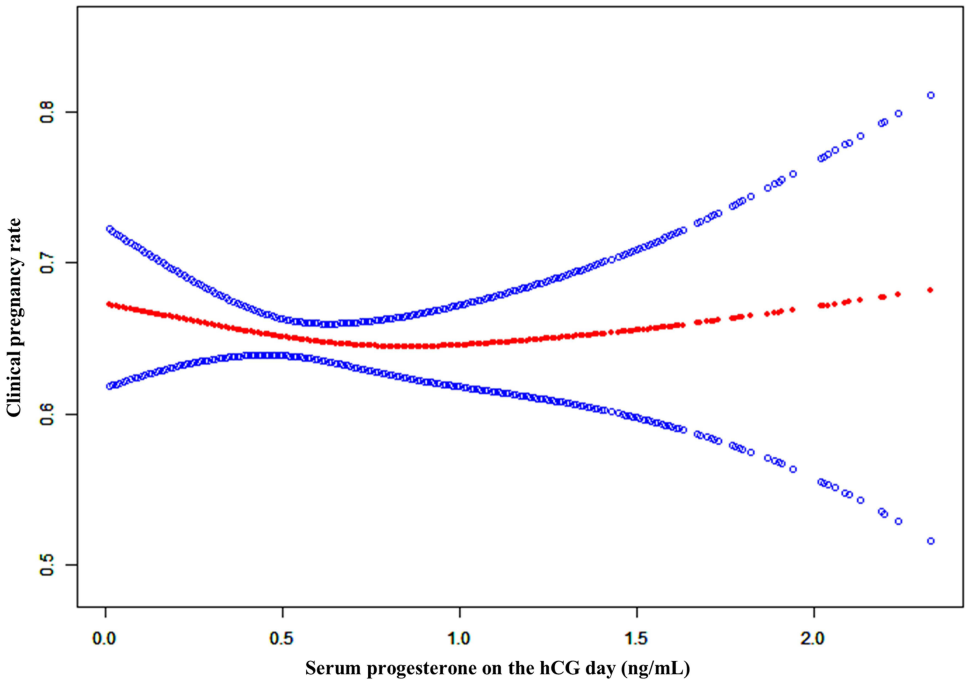

Figure 1 A smooth fitting curve analysis of the relationship between serum P levels on the hCG day and the CPR. The CPR kept stable as the P level increased. The area between two dotted lines is expressed as the 95% CI.

Table 1 Characteristics of Patients with Different Serum P Levels (1.5 ng/mL) on the hCG Day

Variable	Group A	Group B	p value
P Level on Trigger Day (ng/mL)	**≤1.5**	**>1.5**	
Cases (n)	1599	65	
Age (y)	31.2 ± 4.2	30.5 ± 3.6	0.23
BMI (kg/m^2)	22.76 ± 3.16	22.32 ± 2.87	0.09
Basal FSH (mIU/mL)	8.04 ± 2.12	7.75 ± 1.83	0.29
AFC (n)	12.71 ± 4.0	13.3 ± 4.0	0.28
Total Gn dose (IU)	2026.6 ± 580.3	1862.5 ± 572.7	0.16
Gn duration (d)	9.4 ± 1.5	9.4 ± 1.4	0.76
P level on trigger day (ng/mL)	0.60 ± 0.33	1.78 ± 0.22	<0.01
Endometrial thickness (mm)	11.89 ± 2.38	11.43 ± 2.32	0.16
P level after trigger day (ng/mL)	5.15 ± 3.29	7.05 ± 4.32	<0.01
Number of oocytes retrieved (n)	10.1 ± 4.1	11.5 ± 3.6	<0.01
Number of total embryos (n)	4.7 ± 2.4	5.2 ± 2.8	0.29
Number of transferred embryos (n)	1.58 ± 0.49	1.65 ± 0.48	0.28
Types of embryos transferred			0.23
Cleavage-stage embryo (n)	1429 (89.37%)	55 (84.62%)	
Blastocyst (n)	170 (10.63%)	10 (15.38%)	
Embryo implantation rate (%)	53.9 (1361/2525)	56.1 (60/107)	0.74
Clinical pregnancy rate (%)	65.1 (1041/1599)	69.9 (45/65)	0.49
Early miscarriage rate (%)	8.5 (89/1041)	4.4 (2/45)	0.39
Live birth rate (%)	56.2 (898/1599)	61.5 (40/65)	0.45

Abbreviations: P, progesterone; BMI, body mass index; FSH, follicle-stimulating hormone; AFC, antral follicle count; Gn, gonadotropin.

Effect of the Serum P Levels on the CPR for Different Types of Embryos Transfer

A smooth fitting curve was further constructed to investigate the association between serum P levels on the hCG day and the CPR for different types of embryos transfer. As shown in Figure 2, the red line, which represents patients receiving

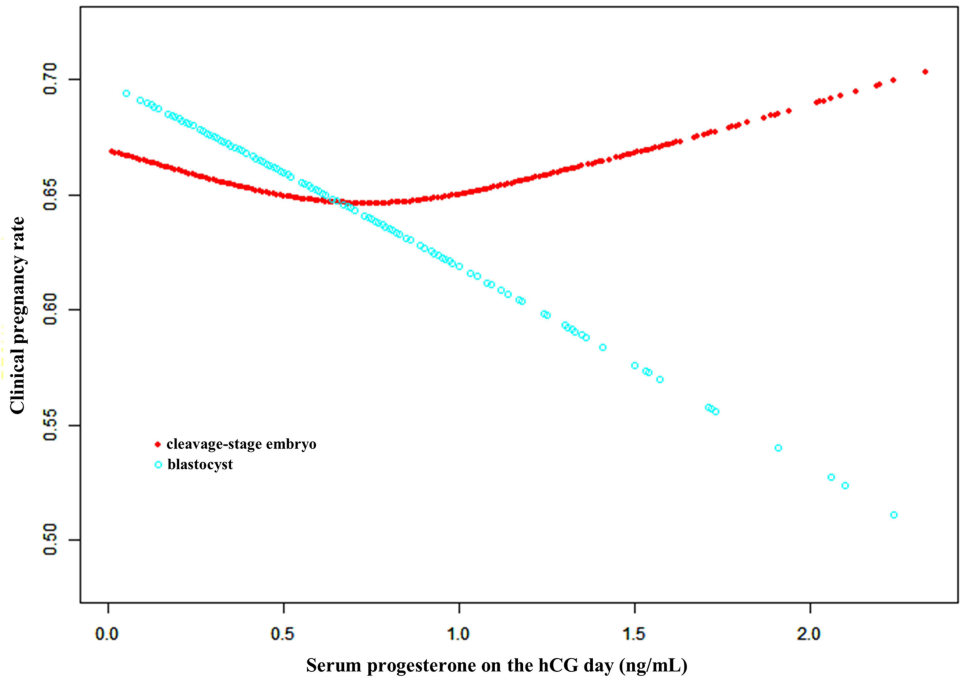

Figure 2 A smooth fitting curve analysis of the relationship between serum P levels on the hCG day and the CPR of different types of embryos transferred. The CPR of blastocyst transfer decreased as the P level on the hCG day gradually increased. The area between two dotted lines is expressed as the 95% CI.

Table 2 Effect Modification of P Levels on the hCG Day on CPR According to Different Types of Embryos Transferred

	Cleavage-Stage Transfer (n=1484)			Blastocyst Transfer (n=180)			P for Interaction
	OR	95% CI	P value	OR	95% CI	P value	
Crude	1.103	0.84–1.45	0.48	0.78	0.34–0.99	0.05	0.09
Adjusted	1.012	0.76–1.35	0.94	0.69	0.34–0.98	0.04	0.04

Notes: Adjust for: Age; BMI; Basal FSH; AFC; Endometrial thickness; Number of transferred embryos.
Abbreviations: P, progesterone; CPR, clinical pregnancy rate; BMI, body mass index; FSH, follicle-stimulating hormone; AFC, antral follicle count.

blastocyst transfer, showed a decline in the CPR with gradually increased serum P levels on the hCG day. In contrast, the CPR of cleavage-stage embryo transfer remained stable as the P level increasing. In addition, an interaction test between the types of embryos and the serum P levels on the CPR was statistically significant (Table 2, P = 0.04).

Discussion

Our study explored the association between serum P levels on the hCG trigger day and the clinical outcomes of short-acting GnRHa IVF-ET cycles. The results showed that the increase in serum P level on the hCG day could significantly reduce the CPR of blastocyst transfer but had no significant effect on the CPR of patients receiving cleavage-stage embryo transfer.

Most previous studies suggested that the increased serum P level on the hCG day had an adverse impact on embryo implantation. A retrospective analysis showed that the pregnancy rate of patients with serum P level of 1.5 ng/mL or above was significantly lower and was not related to COH protocol.[16] In addition, a meta-analysis included 63 studies with a total of more than 60,000 IVF/ICSI cycles, which showed that the increase in serum P levels in late follicular phase had a negative impact on the pregnancy rate of fresh embryo transfer.[18] On the contrary, several studies suggested that the serum P level elevation on the trigger day showed no effect on clinical outcomes.[19–21] To determine whether there is such phenomenon in the IVF cycles of our reproductive medicine centre, we first grouped all data according to different P levels on the hCG trigger day (cut-off value: 1.5 ng/mL). Our study, including 1664 IVF-ET cycles, showed that when the serum P level was greater than 1.5 ng/mL, the CPR of all patients was not significantly decreased. Compared with previous studies, our study only included patients received short-acting GnRHa for pituitary down-regulation, and did not include the GnRH antagonist IVF cycles, in which patients usually received the whole embryo freezing strategy. Additionally, the clinical pregnancy rate reported in previous studies was fluctuating at 30–40%, lower than the conventional clinical pregnancy rate in our centre. This combined with the heterology of infertility patients from different areas might lead to these different conclusions. At present, with the continuous progress of ART technology, the cut-off value of serum P levels on the hCG day in fresh embryo transfer cycles needs to be constantly updated.

Previous studies believed that blastocyst transfer could better tolerate the problem of serum P levels elevation on the day of hCG trigger.[17,22] Therefore, blastocyst transfer is considered as one of the solutions to improve the clinical outcomes of the increased serum P levels on the hCG day.[17,22,23] In this regard, the recent study we published suggested that in the early follicular phase long-acting GnRHa downregulated IVF cycles, the CPR of patients receiving blastocyst transfer decreased with the increase of the P level on the hCG day, which showed that the blastocyst transfer could not conquer the negative effect of the elevated P level.[24] In addition, the COH treatment used in our centre for fresh embryo transfer is mainly the long protocol with long-acting GnRHa or short-acting GnRHa for pituitary downregulation. Therefore, in this retrospective study, we also conducted a subgroup analysis on different types of transferred embryos. We observed a similar phenomenon in the short-acting GnRHa IVF-ET cycles: the adverse influence of elevated serum P levels on the day of hCG trigger on blastocyst transfer. At the same time, there are some previous studies supporting our view.[23,25,26] These inconsistent conclusions remind us that we need to propose corresponding cut-off values of serum P levels for different types of transferred embryos. Therefore, we elementarily explored the potential serum P cut-off value to provide theoretical basis for clinical fresh embryo transfer strategies. When the serum P level is greater than 0.7 ng/mL, the red line (blastocyst transfer) is below the blue line (cleavage-stage embryo transfer) (Figure 2). We re-grouped the serum P levels on the day of hCG trigger (cut-off value: 0.7 ng/mL) and conducted the interaction analysis again for these two

groups. The results suggested that when the serum P level >0.7ng/mL, blastocyst transfer is more vulnerable to the adverse effect of the elevated P level on the hCG day (Table S2), suggesting that cleavage-stage embryo transfer may be a better choice in this condition. However, this hypothesis of P cut-off value and embryo selection for transfer needs to be verified through further prospective studies. Why is blastocyst transfer more susceptible to the increased P levels than cleavage-stage embryo transfer? Studies suggested that increased P levels had adverse effects on the endometrial receptivity.[4–6] The increased P level in advance makes the transformation of endometrium to secretory phase earlier,[4] which leads to the time shift of implantation window and affects embryo implantation. We usually scheduled blastocyst transfer on the fifth day after egg retrieval. The early transformation of the endometrium may lead to the closure of the embryo implantation window at this time, thus causing the failure of blastocyst implantation. The time of embryo transfer at cleavage stage is the third day after egg retrieval, which is easier to match the implantation window of endometrium. In our two studies, we found that the predicted P cut-off value of the long-acting GnRHa IVF cycle is higher than that of the short-acting GnRHa IVF cycle. Previous studies suggested that the pre-treatment of long-acting GnRHa was conducive to the establishment of endometrial receptivity, and the endometrial receptivity of long-acting GnRHa IVF cycle is better than that of short-acting GnRHa IVF cycle.[27,28] We speculate that this may be the possible reason for the different predicted P cut-off values of these two COH protocols. Cleavage-stage embryos transfer has certain advantages in short-acting GnRHa IVF-ET cycles.

The freeze-all policy is also considered as one of the strategies to address the elevated P levels on the hCG day.[23] Some studies suggested that the clinical outcomes of freeze-thaw embryo transfer cycles were similar to or even exceed those of fresh cycle transfer.[29–33] However, the potential risks of the FET cycle cannot be ignored. Studies suggested that there was an increased risk of complications in preeclampsia after the FET cycle,[32] and FET protocols are linked to higher neonatal birth weight and lower risk of low birth weight than fresh embryo transfer.[34,35] The effect of technique on children born from frozen embryos needs long-term follow-up, and more evidence is needed before larger-scale use of embryo freezing.

In addition to above two methods, nowadays there are many other potential strategies that help to achieve successful pregnancy. An increasing number of studies suggested that artificial intelligence (AI) might improve the diagnosis and treatment process of infertility and the clinical outcomes of ART. AI has the potential to be applied in many fields of reproductive medicine, such as follicle monitoring, endometrial receptivity assessment, embryo selection, and prediction of embryonic development after implantation.[36] AI models based on patient clinical features have been trained to help make more effective clinical decisions.[35] According to our studies, progesterone levels on the hCG day may serve as one of important parameters in predicting the outcome of ET, and further mining of AI functions may help find better prevention or solutions to this issue. It is worth noting that not only high quality embryos, proper implantation time and proper physical status are vital points in IVF procedure, psychological condition and many other aspects also counts a lot in a successful ART procedure.[37]

There are still some deficiencies in the current study. Previous studies showed that there were differences in the effect of the increased level of P concentration on the day of hCG trigger on clinical outcomes in women of different ovarian response,[38,39] and the cut-off value of the P level was different.[40] Only the COH protocol of short-acting GnRHa for pituitary down-regulation was included in our study. The ovarian response of these enrolled women is usually at a moderate or slightly low level in our centre. This conclusion is only applicable to the characteristic population. There is a significant difference in the number of patients receiving blastocyst transfer and cleavage-stage embryo transfer. In real life, these results are cautiously applicable. Retrospective design is the main limitation of this study. Further prospective studies are needed to clarify the impact of P level on the hCG day on clinical outcomes.

Conclusions

This retrospective study revealed that elevated serum P levels on the day of hCG trigger in the short-acting GnRHa pituitary downregulated IVF-ET cycle had an adverse effect on blastocyst transfer. When the serum P level was increased on the hCG day, cleavage-stage embryo transfer might be a more reasonable choice than blastocyst transfer, which needs to be confirmed by further prospective clinical studies.

Abbreviations

P, progesterone; COH, controlled ovarian hyperstimulation; CPR, clinical pregnancy rate; IVF-ET, in vitro fertilization-embryo transfer; hCG, human chorionic gonadotropin; GnRHa, gonadotropin-releasing hormone agonist; ICSI,

intracytoplasmic sperm injection; ART, assisted reproductive technology; E_2, oestradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; BMI, body mass index; AFC, antral follicle count; HMG, human menopausal gonadotropin; Gn, gonadotropin; SD, standard deviation.

Data Sharing Statement

The datasets generated and analysed during the current study are not publicly available due to the special requirements of our hospital and our reproductive medicine center for the disclosure of patients' clinical data but are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This retrospective study received ethical approval from the ethics committee of Nanjing Drum Tower Hospital (No. 2023-067-01). All patient couples provided written informed consent. All methods were carried out in accordance with relevant guidelines and regulations.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. Jingwen Jiang, Na Kong and Qingqing Shi should be regarded as joint First Authors.

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Disclosure

The authors declare that they have no competing interests.

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