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Efficacies of different ovarian hyperstimulation protocols in elderly patients with poor ovarian response

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Abstract. – OBJECTIVE: The aim of the study was to explore which controlled ovarian hyperstimulation (COH) protocol is most suitable for elderly patients with poor ovarian response (POR) undergoing assisted reproductive technology (ART).

PATIENTS AND METHODS: This retrospective cohort study evaluated clinical data from 2,660 patients from January 2017 and October 2020. The patients were divided into three groups: modified Gonadotropin-releasing hormone (GnRH) agonist protocol (1,225 patients), GnRH antagonist protocol (1,038 patients), and Mild stimulation protocol (397 patients). Clinical variables and pregnancy outcomes were compared among the three groups.

RESULTS: The GnRH agonist protocol was associated with a higher number of oocyte number (3.99±2.82 *vs.* 3.02±1.34 *vs.* 2.51±1.14, $p<0.001$), a higher number of transferable embryos (1.39±1.32 *vs.* 1.24±1.24 *vs.* 1.18±1.11, $p = 0.035$), higher cumulative live birth rate [26.53% (323/1,225) *vs.* 22.44% (233/1,038) *vs.* 21.66% (86/397), $p = 0.043$], lower OHSS rate [5.14% (63/1,225) *vs.* 3.08% (32/1,038) *vs.* 2.02% (8/397), $p = 0.005$] than GnRH antagonist protocol and Mild stimulation protocol, the Mild stimulation protocol was associated with higher miscarriage rates [30.4% (24/71) *vs.* 25.0% (33/192) *vs.* 29.6% (35/168), $p = 0.014$] than the other two groups.

CONCLUSIONS: The three protocols can be used in elderly patients with POR; however, if patients require more frozen-thawed embryo transfers to achieve better cumulative live birth rates, the modified GnRH agonist protocol may be the better choice. It should be emphasized that the mild stimulation had a slightly higher miscarriage rate than the other two groups.

Key Words:
Poor ovarian response, Age, Controlled ovarian hyperstimulation, Pregnancy outcomes, Assisted reproductive technology.

Introduction

Poor ovarian response (POR) is a significant challenge in assisted reproductive technology (ART), especially for high-age women[1,2]. These women often face difficulties in achieving a successful pregnancy due to decreased ovarian reserve. The tailored controlled ovarian hyperstimulation (COH) protocols are essential for such women to achieve better pregnancy outcomes[3]. There are various approaches to controlling ovarian hyperstimulation, including different gonadotropin preparations, dosages, and durations, as well as the use of adjuvant therapies. However, the optimal protocol remains elusive for older patients with POR[4,5].

COH protocols play a crucial role in ART and significantly affect the successful outcome of *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI) treatment[6]. The ideal ovarian stimulation protocol for high-age women with POR depends on several factors, such as age, ovarian reserve, and previous response to ovarian stimulation[7]. Among the various COH protocols, the GnRH agonist protocol, GnRH antagonist protocol, and mild stimulation protocol have been widely discussed in both international and domestic studies for elderly patients with POR, with significant controversies over their efficacy, safety, and pregnancy outcome[8-10].

The GnRH agonist protocol has been widely utilized in IVF cycles worldwide due to its effectiveness in controlling follicular growth, leading to a predictable, synchronized ovarian stimulation cycle[11,12]. Zhao et al[8] report the superiority of the GnRH agonist protocol over the GnRH antagonist protocol, leading to improved pregnancy rates, reduced ovarian hyperstimulation

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syndrome (OHSS) risk, and improved embryo quality. Nevertheless, Kadoura et al[13] suggest that the GnRH agonist protocol can lead to OHSS, which can affect the success rates of pregnancy outcomes, and, therefore, there are ongoing debates over the efficacy and safety of the GnRH agonist protocol. However, a modified GnRH agonist protocol was used for elderly patients with POR in a preliminary experiment at our center. We named this protocol the early-follicular-phase long-acting GnRH-a long protocol; in the preliminary experiment, pregnancy results were satisfactory, but the data obtained were not sufficient for statistical analysis. Therefore, the present study was conducted.

GnRH antagonist protocols suppress the pituitary gland gonadotropin secretion to prevent premature ovulation. Some studies[14,15] reported that this protocol has a shorter treatment duration, approximating 9-12 days, compared with the agonist protocol, the rapid onset of GnRH antagonists and their short half-lives result in lower E2 levels, potentially reducing the risk of ovarian hyperstimulation syndrome. However, some researchers[16] reported lower live birth rates with the antagonist protocol because of premature corpus luteum regression. Mild stimulation protocols have been developed to reduce the side effects of a high-dose gonadotropin regimen, such as OHSS, premature luteinization, and poor-quality oocytes. However, there are ongoing discussions over the effectiveness of mild stimulation protocols in improving the outcome of assisted reproductive technology[17-19]. Some studies[20,21] indicate that mild stimulation may yield fewer oocytes, reduce the embryo quality, and lower the pregnancy rate compared to high-dose gonadotropin regimens. Further studies on these are therefore needed.

This study aims to discuss the most recent evidence-based recommendations for tailored COH in POR patients and to explore different stimulation protocols and their impact on pregnancy outcomes. Achieving a successful pregnancy for elderly patients with POR patients has become an increasingly important issue, and this study hopes to provide critical insights for clinicians in their treatment planning for these patients.

Patients and Methods

This retrospective cohort study used data from the First People's Hospital of Shangqiu from 1 January 2017 through 30 October 2020. This hospital is the largest tertiary hospital in Shangqiu City, treating an average of 5,000 patients annually for ovulation induction-related diseases. A total of 2,660 elderly patients with poor ovarian response were included in this study.

Inclusion criteria were adult women aged 35 years and above and diagnosed with poor ovarian response according to the Bologna criteria. This study was approved by the Ethics Committee of the First People's Hospital of Shangqiu (SQ20190016; Date: 03.02.2019). The study was a retrospective cohort, and the requirement for informed consent was waived by the Medical Ethics Committee of Shangqiu First People's Hospital. All methods were performed in accordance with the guidelines of the Helsinki Declaration and its latest amendments.

Patients were monitored until December 2022, with the primary objective being the assessment of clinical pregnancy. The medical records of all eligible patients were obtained and examined by two independent investigators. The experimental materials utilized in this study were sourced from the Electronic Medical Record Cohort Database of the Reproductive Medical Center of the First People's Hospital of Shangqiu. Each patient within the database possessed a distinct medical record number. The subjects were randomly allocated to one of three groups using computer-generated randomization based on their medical record number. Routine laboratory tests measuring serum follicle-stimulating hormone, luteinizing hormone, estradiol, and progesterone levels, as well as antral follicle count, were carried out before treatment.

GnRH agonist protocol: On days 2-4 of menstruation, 3.75 mg of GnRH-a (Diphereline, Beaufort-Ipson, France) was administered. In addition, the patients underwent measurement of serum sex hormone levels and ultrasound monitoring. Ovarian stimulation was initiated when the hormone test indicated follicular-stimulating hormone (FSH) < 5 IU/L, luteinizing hormone (LH) < 5 IU/L, estradiol < 30 g/mL, progesterone < 1 ng/mL, and ultrasound monitoring revealed follicle sizes between 3-5 mm; this was achieved by administering recombinant follicle-stimulating hormone (rFSH; Gonal F, Merck Serono, Switzerland) at an initial dosage of 225 IU/day. The dose of FSH was adjusted according to the patient's age, body mass index, ovarian reserve, and previous response to stimulation. Daily transvaginal ultrasonography and serum hormone measurements were

performed to monitor follicular development, and FSH dose adjustments were made accordingly. When one or more follicles reached a mean diameter of 18 mm, 10,000 IU of human chorionic gonadotropin (hCG; Livzon, China) was administered as the trigger for ovulation. After the ovulation trigger, luteal phase support was implemented by administering oral dydrogesterone (Duphaston; Abbott, IL, USA) at a dose of 20 mg twice daily from the day after the ovulation trigger until a negative pregnancy test or up to 12 weeks of gestation if the pregnancy was confirmed.

GnRH antagonist protocol: patients were administered follicle-stimulating hormone (rFSH; Gonal F, Merck Serono, Switzerland) subcutaneously for 5-7 days. The initial dose of FSH was determined by the clinician based on the patient's age, body mass index, and antral follicle count. The dose was adjusted according to the follicular response, which was monitored using transvaginal ultrasound. A gonadotropin-releasing hormone antagonist (Orgalutran, Organon, Netherlands) was added when the leading follicle reached a diameter of 12-14 mm. Cetrorelix or ganirelix was administered subcutaneously once daily until the day of the hCG (Livzon, China) trigger. Transvaginal ultrasound was used to monitor follicular development. When at least three follicles reached a diameter of 18 mm, hCG was administered to trigger ovulation. The dose of hCG was determined by the clinician based on the patient's age, body mass index, and follicular response. Progesterone supplementation was administered to support the luteal phase. Intramuscular injection of progesterone in oil (100 mg/day) or vaginal progesterone gel (90 mg/day) was initiated on the day of oocyte retrieval and continued until 10-14 days after embryo transfer.

Microstimulation: Patients received ovarian stimulation with a microstimulation protocol. Starting on the second day of the menstrual cycle, patients were administered a low dose of follicle-stimulating hormone (rFSH; Gonal F, Merck Serono, Switzerland) subcutaneously for 5-7 days. The initial dose of FSH was 75-150 IU/day, and the dose was adjusted according to the patient's age, body mass index, and antral follicle count. Transvaginal ultrasound was used to monitor follicular development. When at least one follicle reached a diameter of 18 mm, hCG was administered to trigger ovulation. The dose of hCG was determined by the clinician based on the patient's age, body mass index, and follicular response. Progesterone supplementation was administered to support the luteal phase.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. Continuous variables were presented as mean ± standard deviation and compared using one-way analysis of variance (ANOVA) followed by the Bonferroni post-hoc test. Categorical variables were expressed as frequencies and percentages and compared using the Chi-square test or Fisher's exact test, as appropriate. Statistical significance was set at $p < 0.05$.

Results

A total of 2,660 elderly patients with poor ovarian response to IVF/ICSI were included in this study. Of these cycles, GnRH agonist protocol of ovarian stimulation was carried out in 1,225 patients, 935 IVF patients, and 290 ICSI patients. GnRH antagonist protocol of ovarian stimulation was carried out in 1,038 patients, 821 IVF patients, and 217 ICSI patients. Mild stimulation protocol of ovarian stimulation was carried out in 397 patients, 303 IVF patients and 94 ICSI patients. There were no significant differences in baseline characteristics such as age, body mass index, basal follicle-stimulating hormone, basal luteinizing hormone, basal estradiol, anti-Müllerian hormone, thyroid stimulating hormone, serum-free triiodothyronine, and Serum free thyroxine levels among patients who underwent the three protocols (Table I).

The pregnancy outcomes of COH in terms of oocytes and embryos of the three protocols were then compared in each group. the GnRH agonist protocol was associated with a higher total dosage of Gn used (4,042.53±332.7 *vs.* 3,145.63±324.04 [GnRH antagonist] *vs.* 2,642.2±238.30 [Mild stimulation], $p < 0.001$), longer duration of gonadotropin use (14.53±2.57 *vs.* 11.14±2.81 [GnRH antagonist] *vs.* 11.43±2.46 [Mild stimulation], $p < 0.001$), higher number of oocyte number (3.99±2.82 *vs.* 3.02±1.34 [GnRH antagonist] *vs.* 2.51±1.14 [Mild stimulation], $p < 0.001$), higher number of MII number (3.15±2.23 *vs.* 2.55±1.87 [GnRH antagonist] *vs.* 2.01±1.21 [Mild stimulation], $p < 0.001$), higher number of transferable embryos (1.39±1.32 *vs.* 1.24±1.24 *vs.* 1.18±1.11, $p = 0.035$), higher

Table I. Comparison of baseline parameters among the GnRH agonist protocol, GnRH antagonist protocol and mild stimulation protocol.

Protocols	GnRH agonist (n = 1,225)	GnRH antagonist (n = 1,038)	Mild stimulation (n = 397)	*p*-value
Age (years)	39.74 ± 2.61	39.75 ± 2.93	39.65 ± 3.04	0.792
BMI (kg/m^2)	25.24 ± 3.13	25.65 ± 2.76	25.36 ± 2.94	0.261
Basal FSH (IU/L)	10.43 ± 4.14	10.48 ± 4.22	10.87 ± 4.35	0.878
Basal LH (IU/L)	4.66 ± 2.35	4.74 ± 2.16	4.85 ± 2.36	0.953
Basal E2 (ng/L)	43,47 ± 23.32	44.53 ± 30.22	44.68 ± 30.47	0.771
Basal P (μg/L)	0.55 ± 0.34	0.44 ± 0.22	0.49 ± 0.48	0.342
AMH (ng/mL)	0.68 ± 0.34	0.71 ± 0.51	0.63 ± 0.55	0.703
TSH (mlU/ml)	2.15 ± 1.02	2.33 ± 1.11	2.63 ± 1.63	0.590
FT3 (pmol/L)	5.01 ± 0.83	5.63 ± 0.62	5.16 ± 0.46	0.402
FT4 (pmol/L)	11.40 ± 1.81	11.98 ± 1.92	25.6 ± 2.77	0.583
Method of fertilization				0.249
IVF	76.3 (935/1225)	79.1 (821/1038)	76.3 (303/397)	
ICSI	23.7 (290/1225)	20.9 (217/1038)	23.7 (94/397)	

Data are shown as means ± SD or percentages. BMI, body mass index; FSH, follicular-stimulating hormone; LH, luteinizing hormone; E2, estradiol; P, progesterone; AMH, anti-Müllerian hormone; TSH, thyroid stimulating hormone; FT3, serum-free triiodothyronine; FT4, Serum free thyroxine.

number of good-quality embryos (1.33±1.24 *vs.* 1.11±1.12 *vs.* 1.04±0.99, $p = 0.028$), lower OHSS rate [5.14% (63/1225) *vs.* 3.08% (32/1038) *vs.* 2.02% (8/397), $p = 0.005$] than GnRH antagonist protocol and Mild stimulation protocol. There were no differences in the oocyte maturation rates, fresh cycle cancellation rate, and fertilization rates among patients who underwent the three ovarian hyperstimulation protocols (Table II).

The pregnancy outcome of the three protocols in each group was compared, and the mild stimulation protocol was associated with higher miscarriage rates [30.4% (24/71) *vs.* 25.0% (33/192) [GnRH agonist] *vs.* 29.6% (35/168) [GnRH antagonist], $p = 0.014$)], the GnRH agonist protocol was associated with a higher cumulative live birth rate [26.53% (323/1225) *vs.* 22.44% (233/1038) [GnRH antagonist] *vs.* 21.66% (86/397) [Mild stimulation], $p = 0.043$], There were no differences in implantation rates, pregnancy rates per transfer and live birth rates per transfer among patients who underwent the three ovarian hyperstimulation protocols (Table III).

Discussion

Assisted reproductive technology (ART) has proven to be effective in helping many women to solve infertility problems. However, it remains one of the most challenging aspects of fertility treatment to deal with elderly couples who do not respond well

Table II. Comparison of the outcome of COH in terms of oocytes and embryos among the three protocols.

Protocols	GnRH agonist (n = 1,225)	GnRH antagonist (n = 1,038)	Mild stimulation (n = 397)	*p*-value
Total dosage of Gn used (IU)	4042.53 ± 332.7	3145.63 ± 324.04$^{\#}$	2642.2 ± 238.30$^{\#*}$	< 0.001
Duration of Gn used (days)	14.53 ± 2.57	11.14 ± 2.81$^{\#}$	11.43 ± 2.46$^{\#}$	0.022
Oocyte number	3.99 ± 2.82	3.02 ± 1.34$^{\#}$	2.51 ± 1.14$^{\#*}$	< 0.001
MII number	3.15 ± 2.23	2.55 ± 1.87$^{\#}$	2.01 ± 1.21$^{\#*}$	< 0.001
Oocyte maturation rates (%)	81.24 ± 19.11	79.83 ± 22.24	80.31 ± 21.63	0.682
Transferable embryos	1.39 ± 1.32	1.24 ± 1.24$^{\#}$	1.18 ± 1.11$^{\#}$	0.035
Good-quality embryos	1.33 ± 1.24	1.11 ± 1.12$^{\#}$	1.04 ± 0.99$^{\#*}$	0.028
Fresh cycle cancellation Rate (%)	40.71 ± 35.39	42.52 ± 31.41	46.71 ± 40.11	0.913
Fertilization rates (%)	60.34 ± 32.25	55.61 ± 37.45	60.53 ± 38.34	0.162
OHSS rates	5.14 (63/1225)	3.08 (32/1038)$^{\#}$	2.02 (8/397)$^{\#}$	0.005

Data are shown as means ± SD or percentages. MII, metaphase II; OHSS, ovarian hyperstimulate syndrome; $^{\#}p < 0.05$, *vs*. GnRH agonist; $^{*}p < 0.05$, *vs*. GnRH antagonist.

Table III. Comparison of the pregnancy outcome among the three protocols.

Protocols	GnRH agonist (n = 1,225)	GnRH antagonist (n = 1,038)	Mild stimulation (n = 397)	*p*-value
Implantation rates (%)	19.11 (163/853)	19.06 (146/766)	21.52 (51/237)	0.309
Pregnancy rates per transfer (%)	15.67 (192/1225)	16.18 (168/1038)	17.88 (71/397)	0.639
Live birth rates per transfer (%)	12.97 (159/1225)	12.81 (133/1038)	11.83 (47/397)	0.710
Miscarriage rates (%)	25.0 (33/192)	29.6 (35/168)	30.4 (24/71)#*	0.014
Cumulative live birth rates (per cycle)	26.53 (323/1225)	22.44 (233/1038)#	21.66 (86/397)#	0.043

Data are shown as percentages. #$p < 0.05$, *vs*. GnRH agonist; *$p < 0.05$, *vs*. GnRH antagonist.

to ovarian stimulation[22,23]. This study compared the efficacy of three different ovarian hyperstimulation protocols in patients undergoing IVF/ICSI treatment. The absence of significant differences in baseline characteristics among patients undergoing the different ovarian stimulation protocols eliminates the confounding factors that could affect the results of the comparison of the efficacy of these protocols. This ensures that any differences observed in the outcomes are due to the differences in the protocols themselves and not the differences in the baseline characteristics of the patients.

The results showed that the modified GnRH agonist protocol was associated with a higher total dosage of gonadotropin used and longer duration of gonadotropin use compared to the GnRH antagonist and mild stimulation protocols. However, these factors also increase the risk of OHSS. The study showed that the OHSS rate was significantly higher in the GnRH agonist protocol group than in the GnRH antagonist and mild stimulation groups. Prior research has demonstrated a positive correlation between the cumulative dose of gonadotropin and the quantity of oocytes acquired, as well as the number of embryos transplanted, ultimately leading to improved embryo quality, heightened pregnancy rates, and increased live birth rates per transfer[24,25]. However, our study showed that for elderly patients with POR, the pregnancy rates and live birth rates per transfer did not differ significantly among the three protocols, however, if patients require more frozen-thawed embryo transfer to achieve better cumulative live birth rates, it will be necessary to re-evaluate the cost-effectiveness of the modified GnRH agonist protocol. This is due to the fact that the modified GnRH agonist protocol exhibited a significantly higher cumulative live birth rate compared to both the GnRH antagonist and mild stimulation groups. Consequently, we propose the adoption of a modified GnRH agonist protocol for elderly patients with poor ovarian response who require additional embryo transfers to enhance cumulative live birth rates. Of course, it is important to avoid OHSS, a slightly higher proportion of OHSS in the agonist protocol than in the other two protocols. The results suggest that clinicians should consider the individual patient's response to stimulation and choose the most appropriate ovarian hyperstimulation protocol to achieve optimal outcomes with minimal risks.

In addition, it was observed that the mild stimulation protocol was associated with a higher miscarriage rate than the GnRH agonist and GnRH antagonist protocols. Miscarriage has been reported to be associated with various factors, such as maternal age and embryonic chromosomal abnormalities[26,27]. However, the absence of differences in age among patients in the study undergoing the different protocols suggests that the outcomes of these protocols may be comparable in patients of similar age. Similarly, body mass index, basal FSH, LH, estradiol, and AMH levels are also important predictors of ovarian reserve and spontaneous abortion[28,29], however, further studies are required to explore this possibility. On the other hand, the higher cumulative live birth rate observed in the GnRH agonist group is an encouraging finding, a higher cumulative live birth rate indicates that this protocol may help more patients eventually have viable babies. This finding could be attributed to the ability of GnRH agonist to suppress LH secretion, thereby preventing premature ovulation and improving the quality of oocytes obtained[30]. In summary, the study suggests that the Mild stimulation protocol may be associated with a higher miscarriage rate, while the GnRH agonist protocol may be associated with a higher cumulative live birth rate. These findings may provide valuable insights for clinicians when selecting the optimal ovarian hyperstimulation protocol for their patients.

High-age women with POR pose a significant challenge in ART; these women face reduced

ovarian reserve, making it difficult for them to achieve successful pregnancy outcomes. Age may be the most important contributor to oocyte quality and embryo ploidy, which directly influence pregnancy outcomes[3,31]. As known, age is likely to have the most significant impact on oocyte quality and embryo ploidy, both of which are directly related to pregnancy success[32]. For these patients, individualized protocols need to be developed to account for their specific needs. Several studies[33,34] have suggested that one potential approach is the use of recombinant follicle-stimulating hormone (rFSH) instead of urinary-derived preparations and that rFSH can produce a longer-lasting stimulation while reducing the risk of exposure to contaminants. Additionally, the use of GnRH agonist or antagonist can also help to prevent premature ovulation and enhance follicular recruitment, respectively. Adjuvant therapies, such as growth hormone (GH) have also been proposed to improve ovarian response[35]. GH may promote folliculogenesis and improve oocyte quality, potentially enhancing the chances of successful fertilization and implantation[36,37]. However, further studies are needed to confirm these findings.

COH is an essential step in ART, and it involves the administration of exogenous gonadotropins to stimulate multiple follicles[13]. While COH can improve the success rates of ART, choosing the optimal protocol remains a significant challenge for clinicians. This discussion aims to explore the benefits and drawbacks of different COH protocols based on previous research[8,38]. Traditionally, COH protocols have involved the administration of high doses of follicular-stimulating hormone (FSH) and luteinizing hormone (LH) over an extended period. However, this approach can result in excessive oocyte production, ovarian hyperstimulation syndrome, and poor oocyte quality. Moreover, patients receiving gonadotropin stimulation alone may have a higher chance of miscarriage and multiple pregnancies[39,40]. A study conducted by Ni et al[41] demonstrated that adding GnRH antagonist to a GnRH-a protocol significantly improved the pregnancy rate in trigger undergoing ART, reducing the risk of OHSS and multiple pregnancies. Despite the potential benefits of these protocols, however, the success rate of pregnancy is not very high, and the optimal approach for older patients with POR remains unclear[42,43]. Clinicians should consider the individual patient's response to stimulation and choose the most appropriate ovarian hyperstimulation protocol to achieve optimal outcomes with minimal risks.

Limitations

However, the present study has encountered several limitations, namely: (1) the retrospective nature of the study introduces the potential limitation of selection bias. Despite our diligent efforts to screen eligible participants and mitigate confounding factors, the inherent difficulty in completely eliminating this bias persists. (2) The research subjects exclusively consist of Chinese patients undergoing IVF/ICSI, thereby limiting the generalizability and applicability of the findings to a broader population.

Conclusions

There was no difference in fresh-cycle implantation rates or live-birth rates among the three ovarian stimulation regimens in older POR patients. However, if patients require more frozen-thawed embryo transfer to achieve better cumulative live birth rates, the modified GnRH agonist protocol may be the better choice, and it should be emphasized that the Mild stimulation group had a slightly higher miscarriage rate than the other two groups. Further studies including randomized controlled trials are necessary to determine the efficacy of these protocols and their suitability for elderly patients with POR.

Conflict of Interest

The authors declare that they have no conflict of interests.

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Authors' Contribution

X.Y.D., and Z.L. conceived of and designed the experiments. X.Y.D., and M.M.L. selected and supervised suitable patients. X.Y.D., provided overall supervision. X.Y.D., and X.M. drafted the manuscript. All authors reviewed this manuscript.

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Ethics Approval

This study was approved by the Ethics Committee of the First People's Hospital of Shangqiu (SQ20190016).

Informed Consent

The study was a retrospective cohort, and the requirement for informed consent was waived by the Medical Ethics Committee of Shangqiu First People's Hospital (SEE LINE 84-86). (The experimental materials utilized in this study were sourced from the Electronic Medical Record Cohort Database of the Reproductive Medical Center of the First People's Hospital of Shangqiu, China).

Data Availability

The data presented in this study are available on request from the corresponding author.

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