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Clinical effectiveness of different controlled ovarian hyperstimulation schemes on infertility patients with poor ovarian reserve in IVF/ICSI-ET settings

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ABSTRACT

Objective: Patients with poor ovarian reserve usually present with both high cancellation rates in stimulation ovulation cycles and low live birth rates, which represent important clinical challenges in vitro fertilization. Our study aimed to investigate optimal ovarian stimulation via retrospective clinical analysis of pregnancy outcomes achieved by in vitro fertilization/intracytoplasmic sperm injection-embryo transfer (IVF/ICSI-ET) with multiple stimulation schemes in poor ovarian reserves (PORs).

Materials and methods: In this study, we compared 5 regimens for POR patients undergoing IVF/ICSI in Dalian Women & Children's Medical Group and the Affiliated Zhongshan Hospital of Dalian University, Dalian, China, from January 2021 to October 2024 according to Patient-Oriented-Strategies Encompassing Individualized Oocyte Number (POSEIDON) criteria. Patients were classified into progestin-primed ovarian stimulation (PPOS), modified natural, corpus luteum, GnRH antagonist, and minor stimulation groups. Clinical analytic indexes including rates of retrieved oocytes, embryos, fresh embryo transfer cycles, and pregnancy were the main outcomes.

Results: Compared with the other groups, the GnRH antagonist group resulted in higher Gonadotrophin duration, Gonadotrophin dosage, number of oocytes retrieved, and fertilized oocytes. Better clinical outcomes consisting of higher rates of oocytes retrieved, transferable embryos, fresh embryo transfer cycles, embryo implantation, and pregnancy were obtained in the GnRH antagonist group. The modified natural group and minor stimulation group have lower oocytes retrieved number, the startup dose and total amount of gonadotropin is smaller, and the gonadotropin use is shorter, which leads to a decrease in the number of antral follicles, thus reducing the number of oocytes retrieved and available embryos.

Conclusion: The duration and total dose of gonadotropin stimulation were longer and higher in the GnRH antagonist group, but also provided more retrieved and preferential oocytes. In fresh embryo transfer, GnRH antagonists are associated with higher clinical pregnancy.

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Introduction

Delayed childbearing is becoming more and more common in modern society. Due to the natural or pathological aging of the reproductive system, a considerable proportion of women seek in vitro fertilization (IVF) or other assisted reproductive technologies [1, 2]. However, even with the rapid development and advancement of such technologies, women with poor ovarian response (POR) often experience dismal pregnancy rates [1]. Multiple factors such as aging, ovarian surgery, endometriosis, chemo- or radiotherapies, smoking and drinking, and genetic as well as environmental factors could contribute to the development of POR. The European Society of Human Reproduction and Embryology defined and described POR in Bologna criteria in 2011, and subsequently expanded and amended the criteria with the

studies involving the POSEIDON group in 2016 [3, 4]. In the original Bologna criteria, women diagnosed with POR should meet at least two of the three following features: 1) equal or older than 40 years of age or any other risk factor of POR; 2) equal or less than 3 oocytes retrieved after conventional stimulation; and 3) antral follicle count less than 5 to 7 follicles or anti-mullerian hormone level lower than 0.5-1.2 ng/ml[3]. In the revised and amended POSEIDON stratification, the focus has been shifted to oocyte quantification and quality instead of age and other risk factors. In POSEIDON stratification, women of all ages, of their ovarian reserve parameters, could potentially be diagnosed with POR [3].

Clinically, the patients with POR characteristically had fewer retrievable oocytes upon stimulation, lower numbers of transferable embryos, and high cancellation rates of cycles, which ultimately resulted in low clinical pregnancy rates [1, 5, 6]. In recent years, multiple clinical trials have investigated different ovarian stimulation strategies for patients with POR. Either gonadotropin-releasing hormone (GnRH) agonists or antagonists, luteal-phase stimulation, follicular phase stimulation, and other less studied strategies such as minimal ovarian stimulation and modified nature cycles have all been reported to provide benefits to patients with POR [1, 7-10]. Adjunct therapies such as growth hormone, dehydroepiandrosterone, and co-enzyme Q10 have also been reported to be effective in increasing pregnancy rates. However, no consensus has been reached on which strategy has provided the best clinical outcomes. Additional studies are warranted to further analyze the effectiveness of available intervening strategies to identify the optimal options for patients with POR [11-15]. Our study aimed to investigate optimal ovarian stimulation via retrospective clinical analysis of pregnancy outcomes achieved by IVF/ICSI with multiple stimulation protocols in POR.

Materials and Methods

Participants

In this study, we retrospectively investigated POR patients who were admitted to the Reproductive & Genetic Medicine Center, Dalian Women & Children's Medical Group, and the Affiliated Zhongshan Hospital of Dalian University, from January 2018 to November 2021. Patient inclusion criteria were patients who fulfilled the POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) criteria, indicating patients with decreased ovarian reserve aged ≥ 35 years old, AFC ≤ 5 follicles, and AMH < 1.2 ng/mL. Patients with the following were excluded: 1) IVF/ICSI contraindication; 2) endocrine metabolic disease, such as uncontrolled thyroid function, diabetes, hyperandrogenemia; 3) related diseases affecting IVF/ICSI consequence, such as hydrosalpinx, hysteromyoma ≥ 4cm, severe adenomyosis, III or IV stage endometriosis, endometrial lesions (i.e., uterine polyps, mucous fibroids, endometrial echo inhomogeneous); 4) drug allergies applied in this study.

This retrospective study analyzed PORs undergoing IVF-ET ovarian stimulation medication, divided into 5 groups according to its use of the ovulation induction, progestin-primed ovarian stimulation (PPOS) group (634 cycles), modified natural group (300 cycles), corpus luteum stimulation group (335 cycles), the Gonadotropin-releasing hormone (GnRH) antagonist group (2306 cycles), minimal stimulation group (690 cycles), Analyze the clinical ending of 5 kinds of ovulation programs.

Treatment Protocols

All patients underwent reproductive endocrine examination and vaginal ultrasound examination on the second day of menstruation. When no cyst was found in both ovaries, at least one more antral follicle was seen, and the follicle diameter was < 10 mm, the ovulation induction cycle could be entered, otherwise it was canceled. During the ovulation induction cycle, the dosage was adjusted according to the follicle diameter and hormone level. When the follicle diameter was ≥ 18-20 mm, the trigger was given. Oocytes were retrieved trans-vaginally under ultrasound guidance at 35 to 36 hours after the triggering.

PPOS group

From the 2nd day of the menstruation cycle, oral administration of 10 mg/day of Medroxyprogesterone acetate (Xianju, Zhejiang, China) and intramuscular injection with 150-300 IU/d Urofollitropin for Injection, (Livzon, Zhuhai, China) were applied in patients of PPOS group continuously until the trigger day. The dosage of the treatment was adjusted based on follicular diameters and hormonal levels. 10000 IU of HCG trigger injection was carried out when follicular diameters were larger than 18 to 20mm. Ultrasound-guided oocyte retrieval was performed at 35 to 36 hours post-trigger.

Modified natural group

Ultrasound examination was performed for evaluation of antral follicle counts (AFC) and exclusion of bilateral ovarian cysts on the 2nd day of menstruation. Patients presenting endometrium diameter < 5 mm, normal serum basal FSH, LH, E2, and progesterone level subsequently went through modified natural cycles: Vaginal ultrasound examination on the 7th-9th day of menstruation when top-quality embryos diameter reached about 12-14 mm, subcutaneous injection with Cetrorelix Acetate Powder for Injection (Merck-Serono, Germany) 0.25 mg/day until trigger day.

Corpus luteum stimulation group

Ovulation induction was utilized within 2 days from natural cycle ovulation or oocyte retrieval. When the ultrasound examination indicated bilateral ovarian follicles with an average diameter < 8 mm, 225-300 IU/day recombinant human Chorio-gonadotropin alfa treatment (Livzon, Zhuhai, China) *via* intramuscular injection was started until trigger day.

Gonadotropin-releasing hormone antagonist group

In the antagonist group, patients were administered 225-300 IU/d recombinant human Follitropin-Alfa solution for Injection (Gonaffin, Merck-Serono, Germany) from day 2 of menstruation. According to follicular diameter > 14 mm and blood luteinizing hormone (LH) level, antagonist application was subsequently supplemented. Patients received 0.25 mg/day GnRH antagonist (Cetrotide, Merck-Serono, Germany) according to flexible protocol. When follicular diameter reaches at least 18 mm, trigger protocol would be practiced with subcutaneous injection of 0.2 mg of GnRH-a (Triptorelin, Ferring Pharmaceutical, Germany) and Intramuscular injection 2000 IU Recombinant Human Choriogonadotropin alfa for Injection (Livzon, Zhuhai, China).

Minimal stimulation group

Clomifene Citrate Capsules (shanghai Hengshan, China) at a dose of 25-100 mg or letrozole tablets (Hisun, Zhejiang, China) was started on day 2 or 3 of the menstrual period, meanwhile, Urofollitropin for Injection (Livzon, Zhuhai, China) was intramuscularly injected at a dose of 75-150 IU/day. The dosage of the treatment was adjusted based on follicular diameters and hormonal levels. 10000 IU of HCG trigger injection was carried out when follicular diameters were larger than 18 to 20 mm. Ultrasound-guided oocyte retrieval was performed at 35 to 36 hours post-trigger.

IVF/ICSI-ET

Standard IVF/ICSI was performed as appropriate. Zygotes after 22-24h from IVF/ICSI were examined and day-3 embryo morphology was scored. 2 Prokaryotic Nucleus (2PN) zygotes formed blastocyst stage embryos on day 3 and were selected for fresh embryo transfer or vitrification. Fresh embryo transfer choices for patients of the antagonist group, modified natural group, and minor stimulation group were determined according to the endometrium status and personal preference. PPOS group and corpus luteum group embryos were all vitrified.

Luteal phase support and pregnancy evaluation

For luteal phase support, fresh embryo transfer cycles received 60 mg/day progesterone suppositories (Xianju, Zhejiang, China) that were started on the same day of oocyte retrieval. The transfer was performed 3 days later and subsequently patients were injected with (40 mg/time, once/day) progesterone (Xianju, Zhejiang, China), orally administered with Dydrogesterone tablets (10 mg/time, twice/day, Solvay, The Netherlands). The pregnancy outcome was evaluated with serum basal hCG level examination on the 12th-14th day after fresh embryo transfer. Clinical pregnancy was determined as hCG > 2000 mIU/mL and ultrasonographic diagnosis of intrauterine pregnancy sac or ectopic gestational sac.

Statistical analysis

All analyses were performed using SPSS (version 25.0, Chicago, USA). All sample data were normally distributed for continuous values and presented as the mean ± SD. Multi-group ANOVA was conducted to compare single-factor variance. The overall statistical significance was calculated with the POST HOC LSD method for multiple comparisons. The continuity of non-normal distribution is indicated by M (P25, P75) (M indicates median, P indicates percentiles). Comparisons between groups were performed using

Table 1. Baseline demographic and clinical characteristics based on different protocols.

	PPOS(n=634)	Modified Natural(n=300)	Corpus Luteum(n=335)	GnRH antagonist(n=2306)	Minor(n=690)	F/c2	P
Age (years)	38.38±4.78	39.43±5.06	38.4±4.81	38.48±4.56	38.38±4.93	2.175	0.069
Type of infertility							
Primary infertility	311(49.05)	146(48.67)	154(45.97)	1146(49.70)	348(50.43)	3.746	0.441
Secondary infertility	323(50.95)	154(51.33)	181(54.03)	1160(50.30)	342(49.57)		
Duration of infertility(years)	3.00(2.00,5.00)	2.00(1.00,5.00)	2.00(1.00,4.00)	3.00(1.00,5.00)	3.00(1.50,5.00)	6.24	0.182
BMI (kg/m2)	22.84±3.49	23.04±2.92	23.09±3.1	23.28±3.71	23.45±3.76	2.11	0.077
Basal E2(pg/mL)	37.07(24.82,55.73)	37.23(24.52,55.04)	41.2(27.16,60.65)	39.62(27.98,54.89)	37.49(24.87,54.59)	9.354	0.054
Basal LH(mIU/mL)	4.47(3.31,6.14)	4.75(3.39,6.71)	4.54(3.29,5.74)	4.52(3.24,6.04)	4.64(3.23,6.64)	2.335	0.674
Basal FSH(mIU/mL)	10.11±4.83	10.77±4.45	10.17±4.51	10.25±5.17	10.86±5.32	1.991	0.093
AMH(ng/mL)	0.78±0.43	0.77±0.42	0.77±0.43	0.81±0.44	0.76±0.46	2.149	0.072
Antral follicle counts	2.96±1.42	2.93±1.44	2.98±1.45	3.01±1.42	3.08±1.38	0.561	0.691

Note: Values expressed as median (interquartile range), BMI Body Mass Index, AMH anti-müllerian hormone, FSH follicle stimulating hormone, LH luteinizing hormone, E2 estradiol

Table 2. Cycle characteristics according to different protocols.

	PPOS	Modified Natural	Corpus Luteum	GnRH-a	Minor	F/c2	P
Gonadotrophin duration(days)	8.81±2.21	5.01±2.67*	7.77±2.60*#	8.82±2.39#	5.39±2.60*△※	270.277	<0.001
Gonadotrophin dosage(U)	2828.98± 1043.39	1597.04± 1013.59*	2255.91± 1223.73*#	2882.8±1234.08#	1009.83± 849.28*#△※	285.583	<0.001
Number of oocytes retrieved	3.36±2.42	1.49±0.93*	2.82±1.86*#	3.77±2.39*#	2.07±1.36*#△※	93.978	<0.001
Number of fertilized oocytes	2.52±2.05	1.02±0.89*	2.14±1.70*#	2.75±2.05*#	1.50±1.27*#△※	70.402	<0.001
Good-quality embryos	0.00 (0.00,1.00)	0.00 (0.00,1.00)*	1.00 (0.00,2.00)#	1.00 (0.00,2.00)*#	0.00 (0.00,1.00)*# △※	96.842	<0.001
E2 on hCG day (pg/mL)	921.5 (519.95,1491)	365.85 (265.9,539)*	848.9 (486.2,1286.75)#	978.95 (577.75,1585.25)#	286 (125.03,646.48)*# △※	627.607	<0.001
LH on hCG day(mIU/mL)	3.41 (1.97,5.41)	6.39 (3.96,9.84)*	2.12 (1.15,4.24)*#	3.66 (2.28,5.98)*#	5.75(3.63,8.87)* △※	289.656	<0.001
Endometrial thickness on hCG day(mm)	6.59±2.62	8.34±3.07*	8.38±3.47*	8.98±2.93*#	6.12±3.18*# △※	119.108	<0.001

Note: *means compared with PPOS P<0.05,#means compared with Modified Natural P<0.05,△means compared with Corpus Luteum P<0.05, ※means compared with Anti P<0.05

the Man-Whitney U test. Significance was defined as a p-value < 0.05.

Result

Patients according to POSEIDON criteria were included in our study, of whom were classified into 5 groups conducting different stimulation protocols, 630, 300, 335, 2306, and 690 women undergoing PPOS, modified natural, corpus luteum protocol, GnRH antagonist and minor stimulation, respectively. The findings revealed that demographic parameters, including mean age, type of infertility, duration of infertility, body mass index (BMI), antral follicle counts (AFC), serum AMH, and basal hormonal levels, were similar in 5 groups (Table 1).

PPOS and GnRH antagonist groups were characterized by significantly longer durations of gonadotropin stimulation days, a higher total dose of gonadotropin, a higher number of oocytes retrieved and fertilized oocytes, higher peak E_2 than other protocols at the trigger day, followed by corpus luteum group. Corpus luteum and GnRH antagonist groups resulted in statistically significant higher numbers of good-quality embryos through analysis of non-normal continuity distribution, both groups were indicated by 1.00 (0.00, 2.00). The endometrial thickness on the trigger day of Modified natural, corpus luteum, and GnRH antagonist cycles were significantly higher than PPOS and minor cycles. Meanwhile, the luteinizing hormone (LH) levels in corpus luteum groups came out with the lowest LH level on trigger day (Table 2, Figure 1).

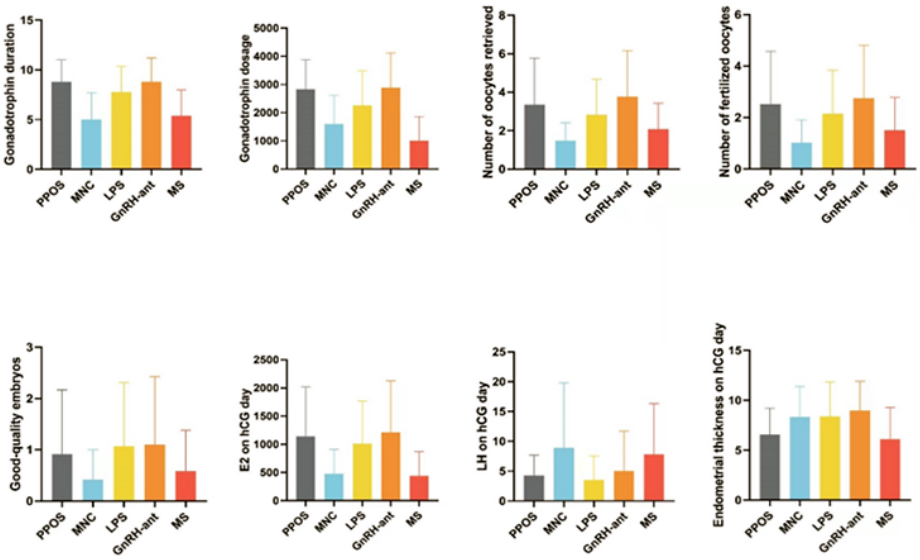

Figure 1. Cycle characteristics according to different protocols. Abbreviations: PPOS: progestin-primed ovarian stimulation group; MNC: modified natural group; LPS: corpus luteum group; GnRH-ant: GnRH-antagonist group; MS: minor stimulation group. Color code: Gray: PPOS; Blue: MNC; Yellow: LPS; Orange: GnRH-ant; Red: MS.

Table 3. Clinical outcomes according to different protocols.

Rates (%)	PPOS	Modified Natural	Corpus Luteum	GnRH-a	Minor	F/c2	P
Rate of early ovulation (%)	7(1.10)	31(10.33)a	12(3.58)ab	43(1.86)b	20(2.90)b	81.345	<0.001
Oocytes retrieved (%)	618(97.48)	275(91.67) a	316(94.33)	2256(97.83) bc	648(93.91) ad	52.032	<0.001
Available embryos (%)	531(83.75)	226(75.33) a	277(82.69)	1982(85.95) b	553(80.14) d	30.563	<0.001
Rate of fresh embryo transfer cycles (%)	0(0)	5(1.67)a	0(0)	340(14.74)abc	13(1.88)ad	262.596	<0.001
Embryo implantation rate(%)	0(0)	2(40)	0(0)	165(48.53)abc	6(46.15)d	121.13	<0.001
Clinical pregnancy rate (%)	0(0)	2(40)	0(0)	165(48.53)abc	6(46.15)d	124.734	<0.001
Early abortion rate (%)	0(0)	1(50)	0(0)	51(30.91)a	3(50)d	—	<0.001#

Note: A means compared with PPOS P<0.005,b means compared with Modified Natural P<0.005,c means compared with Corpus Luteum P<0.005,d means compared with Anti P<0.005

There are 7, 31, 12, 43, and 20 cycles in 5 groups, respectively, of early ovulation noted during the oocyte retrieval procedures in IVF/ICSI cycles. Rates of percentages in PPOs, modified natural, corpus luteum, GnRH antagonist, and minor groups were 1.10%, 10.33%, 3.58%, 1.86%and 2.90%, respectively, and the modified natural group was significantly higher than other groups (Table 3). Early ovulation rates were comparatively higher in the modified natural group. The clinical outcomes of the GnRH antagonist group including the rates of oocytes retrieved (97.83%), available embryos (85.95%), fresh embryo transfer cycles (14.74%), embryo implantation (48.53%), and clinical pregnancy (48.53%) were higher than all other four groups (Table 3). The cycles of early abortion in the minor stimulation group and GnRH antagonist group were 3 and 51, of which counted into rates of 50% and 30.91%, respectively (Tab 3).

Discussion

Numerous stimulation protocols have been utilized in the efforts to carry out in vitro fertilization for patients with POR, including but not limited to progestin-primed ovarian stimulation, modified natural stimulation, corpus luteum stimulation, gonadotropin-releasing hormone antagonist protocol, and minimal stimulation protocol. However, despite years of clinical research, there is no consensus on which protocol provides the optimal benefits for

PORs [7-16]. Additional studies are warranted to examine and compare the efficacy of different simulation protocols. Further, the POSEIDON stratification of patients with POR has been widely accepted since its establishment in 2016 [3, 4]. POSEIDON stratification expanded the definition and inclusion criteria of patients with POR while dividing the patients into subgroups based on their age and ovarian reserve. As a result, studies aimed to examine the effects of different stimulation protocols on specific subgroups of patients are also warranted [3, 4].

In this retrospective study, we examined and compared the efficacy of 5 regimens for patients with POR who undergoing IVF from January 2018 to November 2021. These patients are within Group 4 according to POSEIDON criteria, with age older than 35, AFC less than 5, and AMH levels lower than 1.2 ng/mL. The 5 regimens include progestin-primed ovarian stimulation (PPOS), modified natural, corpus luteum, GnRH antagonist, and minimal stimulation groups. Clinical indexes including rates of retrieved oocytes, available embryos, fresh embryo transfer cycles, and pregnancy were the main outcomes. Our results revealed that, compared to the other 4 regimens, the GnRH antagonist regimen results in a significant increase in the duration and dosage of gonadotropin. The use of GnRH antagonists in the mid or late-follicle stage drastically inhibits the normal function of the pituitary, which in turn, diminishes the release of FSH and LH, resulting in slower development of the follicle and lower levels of estrogen, all of which require increased duration and dosage of gonadotrophin. On the other hand, the use of clomiphene and letrozole in the minimal stimulation regimen enhanced the release of FSH and LH from the pituitary gland, hence the shortest duration and lowest dosage of gonadotrophin needed.

Further, our data suggests that the number of retrievable oocytes, fertilized oocytes, and embryos with good quality are directly correlated with the duration and dosage of gonadotrophin that promotes the growth and maturation of follicles. In the GnRH antagonist group, patients received the highest dosage of gonadotrophin for the longest duration. As a result, we were able to retrieve the highest numbers of oocytes and viable embryos from patients who received GnRH-antagonist treatment. On the other hand, patients in the modified natural group received the lowest dosage of gonadotrophin for the shortest duration, hence the lowest number of retrievable oocytes.

In terms of early ovulation rate, non-retrievable oocytes, or non-viable embryos, the modified natural regimen produced the highest non-retrievable oocyte rate while the GnRH-antagonist and PPOS regimens had the lowest. Moreover, we found that the GnRH antagonist regimen led to a higher number of retrieved oocytes, more successful insemination, as well as better quality of embryos when compared to the other 4 regimens.

LH plays a vital role in the development and maturation of follicles. Reduction in LH levels may lead to increased generation of testosterone while lowering the production of estrogen, which may cause dysfunction in the follicular microenvironment and ultimately result in follicles with poor quality. However, in IVF, reduced LH could limit the risk of early excretion of the oocytes. Our analysis revealed that all 5 regimens regulate LH levels, probably through different mechanisms. For example, clomiphene blocks the binding of estrogen to estrogen receptors, hence the reduction in the positive-regulative effects of estrogen on LH; high levels of progestin on the other hand, suppress the activity of the hypothalamus and pituitary through a negative feedback mechanism, causing reduced FSH and LH release; further, The effect of GnRH-antagonist on inhibiting early-onset LH peak is more obvious, and the down-regulation effect is better, so that the follicles develop evenly, to obtain better embryo. The pituitary inhibition is stronger, which may help to improve the oocyte retrieval rate. The use of GnRH-antagonist in the late stage of follicular development can not only inhibit the formation of endogenous LH peak but also avoid the inhibition of follicular recruitment in the early follicular phase, which can make the follicles better natural recruitment.

Conclusion

In conclusion, our results compared the clinical indicators of different ovulation induction regimens in patients with diminished ovarian reserve. The duration and total dose of gonadotrophin stimulation were longer and higher in the GnRH antagonist group but also provided more retrieved preferential oocytes. After fresh embryo transfer, GnRH antagonist group was associated with higher clinical pregnancy and lower early abortion rates.

Conflict of Interest

All authors declare no conflict of interest.

Ethics Approval and consent to participate

This project was approved by the Ethics Committee of Dalian Women & Children's Medical Group and the Affiliated Zhongshan Hospital of Dalian University.

Consent for Publication

No identifying information about participants is contained in the manuscript or the data collection.

Availability of data and material

The raw data supporting the conclusions of this article will be made available upon request.

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Contribution

HD designed the project, collected, and analyzed the data, and drafted the manuscript; JZ designed and oversaw the project, revised, and finalized the manuscript, and provided funding for their support in collecting the data.

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