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Original Research

The Clinical Pregnancy Rate of Ethinylestradiol/Cyproterone Acetate Downregulation Protocol Is Not Inferior to That of the Conventional Gonadotropin-Releasing Hormone-Analogs Downregulation Group: A Randomized Controlled Trial

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Abstract

Background: Downregulation of the hypothalamic/pituitary axis is a critical step in patients undergoing controlled ovarian hyperstimulation (COH). The aim of this study was to compare clinical pregnancy rates between gonadotropin-releasing hormone-analogs (GnRH-a) and ethinylestradiol/cyproterone acetate (EE/CPA) downregulation protocols in assisted reproductive technology (ART). **Methods**: A total of 392 patients received EE/CPA, while 392 patients were treated with Triptorelin Acetate (0.1 mg) or Diphereline as the control group. 1–2 embryos were transferred, and the primary outcome measure was the clinical pregnancy rate. Secondary outcomes included the number of oocytes, mature oocytes, fertilized oocytes, good-quality embryos, mature oocyte rate, fertilization rate, cleavage rate, viable embryo rate, good-quality embryo rate, implantation rate, and the incidence of ovarian hyperstimulation syndrome (OHSS). In addition, the economic cost was compared between groups. **Results**: There were no significant differences in the clinical pregnancy rates between the EE/CPA and control groups (50.4% vs. 51.9%, $p = 0.630$). In the EE/CPA group, the numbers of oocytes retrieved (14.67 vs. 14.78, $p = 0.809$), mature oocytes (12.95 vs. 13.24, $p = 0.459$), fertilized oocytes (11.59 vs. 12.11, $p = 0.154$), viable embryo rate (47.5% vs. 49.2%, $p = 0.099$), good-quality embryos (4.98 vs. 5.19, $p = 0.311$), good-quality embryos rate (43.0% vs. 42.8%, $p = 0.846$), as well as the implantation rate (37.0% vs. 38.0%, $p = 0.741$), were comparable to those of the control group. The mature oocyte rate (88.3% vs. 89.6%, $p = 0.023$), fertilization rate (89.5% vs. 91.5%, $p < 0.001$), number of viable embryos (5.51 vs. 5.96, $p = 0.026$) were lower than that in the control group, while the cleavage rate (98.0% vs. 96.8%, $p < 0.001$) was higher. The incidence of OHSS was significantly lower in EE/CPA group (0.0% vs. 2.0%, $p = 0.008$). The economic cost of the EE/CPA group was significantly lower than that in the control group. **Conclusions**: Compared with the GnRH-a downregulation protocol, the EE/CPA protocol yielded comparable outcomes. Thus, EE/CPA may represent a viable alternative for COH, offering greater flexibility and lower cost. **Clinical Trial Registration**: The study has been registered on: https://www.chictr.org.cn/ (registration number: ChiCTR2100048310; registration link: https://www.chictr.org.cn/showproj.html?proj=125733).

Keywords: ethinylestradiol/cyproterone acetate; randomized controlled trial; downregulation; assisted reproductive technology

1. Introduction

It is well-known that luteinizing hormone (LH) may have an effect on oocyte quality. As a result, the process of hypothalamic/pituitary downregulation is crucial for the clinical outcomes of patients undergoing controlled ovarian hyper-stimulation (COH) for *in vitro* fertilization (IVF). For the downregulation protocol, the majority of physicians focus on gonadotropin-releasing hormone-analogs (GnRH-a)/GnRH antagonists. In addition, the time point of GnRH treatment is relatively fixed, and it is administered by subcutaneous injection on the 2nd to 5th day of the menstrual cycle. The down-regulation of GnRH-a traditionally makes developmental synchronization of the antral follicle. However, there are some shortcomings. On the one hand, it is due to the discomfort caused by the subcutaneous injection of drugs; on the other hand, the cost of the drug is high. More importantly, some patients will inevitably develop ovarian hyperstimulation syndrome (OHSS) [1]. Therefore, it is particularly important to find a drug that is cost-effective, safe, and convenient to use.

Ethinylestradiol/cyproterone acetate (EE/CPA), named as Diane-35, has dual effects of antiandrogenic and

inhibiting the pituitary gland. It is particularly effective in reducing LH surges and stabilizing ovarian responses. The premature LH-induced meiosis may disrupt follicular development, and the intervention aims to prevent the impairment [2]. Unlike other combined oral contraceptives (COCs), EE/CPA has been proven effective for people with polycystic ovary syndrome (PCOS). Hwang *et al*. [3] proposed a stimulation protocol for women with PCOS, using EE/CPA pretreatment and cetrorelix. The pregnancy outcome they obtained was similar to that of the GnRH agonist protocol used for fresh embryo transfer [3]. This indicates that EE/CPA may have wider applicability in the COH protocols. Although other COCs mainly inhibit ovulation through the synergistic effect of estrogen and progesterone (P), the cyproterone component of EE/CPA directly targets androgen excess and may improve follicular synchronization in non-PCOS populations.

The present study was conducted to investigate the effects of the EE/CPA downregulation stimulation protocol in IVF, compared with GnRH-a. The primary outcome was clinical pregnancy rate, and the secondary outcome was quality of oocytes, including the meiosis stage II (MII) rate, fertilization rate, the number of good-quality embryos, fertilization rate, cleavage rate, viable embryo rate, good-quality embryos rate, and implantation rate. In addition, the economic cost was analyzed.

2. Materials and Methods

2.1 Patients

The present randomized controlled trial (RCT) included infertile patients undergoing their first IVF/intracytoplasmic sperm injection (ICSI)-frozen-thawed embryo transfer (FET) cycles from July to December 2021. Oocyte retrieval and *in vitro* culture were performed at the Center of Reproductive Medicine of the Children's Hospital of Shanxi and Women Health Center of Shanxi. The study has been registered on: https://www.chictr.org.cn/ (registration number: ChiCTR2100048310; registration link: https://www.chictr.org.cn/showproj.html?proj=125733). The present study was approved by the Ethics Committee of Children's Hospital of Shanxi and Women Health Center of Shanxi (approval number: IRB-KYYN-2021-00478). The patients were recruited based on specified inclusion criteria after signing informed consent forms. The inclusion criteria were as follows: (1) The patients had to be on their first IVF cycle; (2) Females aged $<$35 years; (3) Baseline serum follicle-stimulating hormone (FSH) concentration $<$15 U/L; (4) $>$5 antral follicles had to be obtained on days 2–3 of menstruation. The following exclusion criteria were used: (1) PCOS; (2) Endometriosis Grade I or above; (3) Congenital abnormal uterine development; (4) Have received hormone therapy in the past 1 month; (5) History of previous pregnancy/recurrent pregnancy loss/prior abortions.

2.2 Randomization

All eligible females were randomly allocated to the EE/CPA and control groups. A randomization table was generated using the computer application. Due to the different routes of drug administration (oral vs. injection), blinding was impossible. However, the investigators and embryologists were blinded.

2.3 Study Protocol

The present study was a prospective RCT comparing the EE/CPA oral contraceptive protocol with the conventional ovarian stimulation protocol as regards pregnancy outcomes and oocyte quality. The study subjects were randomly divided into two study arms as follows:

(1) Downregulation began on the second day of the menstrual cycle with the oral administration of EE/CPA (Schering GmbH & Co. Produktions KG, J20140114, Leverkusen, North Rhine-Westphalia, Germany) at 1 tablet/day in the EE/CPA group. Follicular monitoring by ultrasonography commenced on 8th menstrual day. On the same day, the serum concentrations of FSH, LH, estradiol (E2) and P were measured. Downregulation was confirmed by transvaginal ultrasound (follicle diameter $\leq$5 mm, endometrial thickness $<$5 mm) and serum hormone levels (LH $\leq$5 mIU/mL, E2 $\leq$50 pg/mL, P $\leq$1.5 ng/mL). The gonadotropin (Gn) dose needs to comprehensively consider age, antral follicular count (AFC), body mass index (BMI) and patient-oriented strategies encompassing individualized oocyte number (POSEIDON) to optimize ovarian response and pregnancy outcome [4].

(2) Patients in the control group received either (1) short-acting triptorelin acetate (H20093852, Lizhu Pharmaceutical Trading Co., P.R., Zhuhai, Guangdong, China, 0.1 mg/day subcutaneous) administered in the mid-luteal phase until the day of human chorionic gonadotropin (hCG) administration or (2) long-acting diphereline (H20194086, Lizhu Pharmaceutical Trading Co., P.R., Zhuhai, Guangdong, China, 1.88 mg intramuscular, single dose) administered in the mid-luteal phase. After 14 days, stimulation was commenced after the women reached the downregulation criteria. The Gn was injected. Subgroup analysis confirmed that there was no significant difference in the results between short-acting and long-acting GnRH-a, proving the rationality of the combined analysis.

In both groups, the final stage of oocyte maturation was triggered by 10,000 IU hCG when the follicles ($\geq$3) reached 16 mm in diameter or the dominant follicle reached 18 mm in diameter. Transvaginal ultrasound-guided oocyte retrieval was conducted at 36 h after the hCG trigger. All follicles $>$10 mm in diameter were aspirated [3]. Oocytes were inseminated by conventional IVF or ICSI, depending on the quality of the semen [5]. Fertilization was determined by observing pronuclei at 18 h and embryo cleavage was observed at 72 h following oocyte retrieval. The embryos were cultured in G-1 PLUSTM medium (10128,

Vitrolife Sweden AB, Goteborg, Sweden) at 37 °C in a humidified 6% CO_2 incubator. Embryo quality was evaluated according to the number and regularity of blastomeres of the embryos and the degree of embryonic fragmentation according to published criteria as follows [6]. Grade I, cells of equal size, regular shape, complete zona pellucida, uniform and clear cytoplasm, no granulation, cytoplasmic fragmentation <5%; grade II, cells of slightly unequal size and irregular shape, some granulation, 10–20% cytoplasmic fragmentation; grade III, cells of an obviously unequal size and irregular shape, significant granulation, 21–50% cytoplasmic fragmentation; grade IV, cells with a markedly unequal size, severe granulation and cytoplasmic fragmentation >50%. Blastocysts were observed at 120 h and graded according to the criteria described by Gardner. All good-quality embryos (grades I and II) were frozen on day 3 following oocyte retrieval. The remaining embryos were cultured until the blastocyst stage. Cleavage-stage embryos and blastocysts were frozen by vitrification. Vitrification cryopreservation is a rapid method for freezing cells or tissues, which can prevent the formation of ice crystals within cells during the freeze-thaw process and minimize cell damage to the greatest extent.

According to the patient's endometrium, the level of P and embryo score, the thawed 1–2 embryos/blastocysts were transferred during hormone replacement treatment cycles. The freezing strategy was adopted in all cycles to eliminate the confusing effect of fresh transplantation and frozen transplantation on endometrial receptivity. Although the GnRH-a protocol traditionally allows for fresh transplantation, this design ensures comparability between groups by standardizing embryo transfer conditions. Dydrogesterone is used to correct P insufficiency, ensuring luteal support for the embryo during the critical window period (prior to 10 weeks of gestation). This regimen optimizes therapeutic efficacy while minimizing risks; however, clinical implementation must be guided by individualized assessment.

2.4 Definition of Outcomes

The primary outcome was the clinical pregnancy rates per embryo transfer, defined as the presence of at least one intrauterine gestational sac with fetal cardiac activity confirmed by transvaginal ultrasound at 7 weeks of gestation [7]. The secondary outcomes were the numbers of oocyte, mature oocytes, normally fertilized oocytes, good-quality embryos, oocyte retrieval rate, mature oocyte rate, normal fertilization rate, cleavage rate and implantation rate. Clinical pregnancy was defined as the presence of a fetal heartbeat observed by transvaginal ultrasonography 4 weeks following FET. The implantation rate was defined as the ratio of the number of gestational sacs to the number of embryos transferred. OHSS was a complication of ART, whose diagnostic criteria was based on the references [8].

2.5 Sample Size Calculation

Sample size was calculated for a noninferiority trial of the two groups at a ratio of 1:1. Compared with the clinical pregnancy rates in the traditional ovulation induction protocol, a proportion of 50% was considered non-inferior. A total of 392 patients per group are required to exhibit non-inferiority with 80% power and a one-sided significance level alpha of 0.025. Accounting for 2% loss-to-follow up, oocyte and embryo were not obtained, 400 patients would need to be included per group, with 800 patients in total. The patients withdrew from the study due to adverse reactions.

2.6 Statistical Analysis

All analyses were performed using IBM SPSS Statistics (v. 18.0, IBM Corp., Armonk, NY, USA). Numerical data are presented as the mean ± standard deviation, and categorical data are presented as number (n) and percentage (%). The Student's *t*-test was used for data with normal distribution between two groups. The chi-squared test was used for categorical data with expected frequencies were >5. The Fisher's exact test was for categorical data with expected frequencies were <5. $p < 0.05$ was considered to indicate a statistically significant difference.

3. Results

3.1 Basic Data of Infertility Couples

In total, 784 participants were enrolled in the present study. The results are presented in Table 1. There was no significant difference in basic data between the EE/CPA and control group, other than the incidence of OHSS. The incidence of OHSS was significantly lower in the EE/CPA group than in the control group ($p = 0.008$).

3.2 Comparison of Outcome Indicators

The primary outcomes are presented in Table 2. The implantation rate per FET was 214/578 (37.0%) in the EE/CPA group and 230/606 (38.0%) in the control group. And, the clinical pregnancy rate per transfer 240/476 (50.4%) in the EE/CPA group was similar to that of the control group 266/512 (51.9%). There was no significant difference ($p > 0.05$) between the two groups.

The secondary outcomes in both groups are presented in Table 3. Similar results were obtained in both the EE/CPA and control group. The doses and treatment durations of Gn in the EE/CPA group were slightly higher than those in the control group. The mean number of oocytes retrieved, MII oocyte, fertilized oocytes, cleavage and good-quality embryos in the EE/CPA group were comparable to those in the control group. Of note, the number of viable embryos, mature oocyte rate and fertilization rate in the EE/CPA group were lower than that in the control group, while the cleavage rate was higher ($p < 0.05$). There was no significant difference in the good-quality embryo rate between the groups.

Table 1. Basic characteristics of the two COH groups.

Parameters	EE/CPA group (n = 392)	Control group (n = 392)	*p*-value
Maternal Age (years)	30.22 ± 3.14	30.23 ± 3.15	0.964
BMI (kg/m^2)	22.79 ± 3.26	23.11 ± 3.39	0.169
Type of infertility			0.883
Primary	245 (62.5%)	243 (62.0%)	
Secondary	147 (37.5%)	149 (38.0%)	
Infertility duration (years)	3.81 ± 2.57	3.86 ± 2.50	0.761
Endocrine profile			
Prolactin (ng/mL)	15.61 ± 8.56	15.44 ± 9.27	0.794
FSH (mU/mL)	8.88 ± 3.04	8.68 ± 3.26	0.383
LH (mU/mL)	5.30 ± 2.49	5.26 ± 2.61	0.799
E2 (pg/mL)	71.17 ± 24.07	66.84 ± 40.93	0.072
P (ng/mL)	0.87 ± 0.46	0.93 ± 0.56	0.078
Testosterone (ng/mL)	46.41 ± 19.55	49.62 ± 28.97	0.069
Reason for infertility			0.163
Tubal (%)	233 (59.4%)	208 (53.1%)	
Male factors (%)	71 (18.1%)	76 (19.4%)	
Others	88 (22.5%)	108 (27.5%)	
Moderate or severe OHSS (%)	0 (0.0%)	8 (2.0%)	0.008

Dates were expressed as the mean ± standard deviation or number (%).

Differences between the groups were analyzed by the Student's *t*-test, chi-squared test or Fisher's exact test.

EE/CPA, ethinylestradiol/cyproterone acetate; OHSS, ovarian hyperstimulation syndrome; LH, luteinizing hormone; FSH, follicle-stimulating hormone; E2, estradiol; P, progesterone; COH, controlled ovarian hyperstimulation; BMI, body mass index.

Table 2. Comparison of pregnancy outcomes.

Pregnancy outcomes	EE/CPA group	Control group	*p*-value
Implantation rate (%)	214 (37.0)	230 (38.0)	0.741
Clinical pregnancy rate (%)	240 (50.4)	266 (51.9)	0.630

Dates were expressed as the number (%).

Differences between the groups were analyzed by the chi-squared test.

3.3 Economic Cost

Total costs included medications (EE/CPA, GnRH-a, Gns), monitoring, and FET expenses. The cost of EE/CPA was significantly lower than that of short-acting/long-acting GnRH-a for conventional COH protocols (Table 4). Although the dosage and duration of Gn in the EE/CPA group were slightly higher than those in the control group, the cost difference between the two groups was not significant. The cost of FET was equivalent between groups. The total costs remained lower due to the GnRH-a expense in the EE/CPA group.

4. Discussion

During the procedure of IVF, excessive doses of GnRH-a prolong the recovery of the pituitary gland and require higher doses of Gns to overcome the inhibition of follicular development [9]. EE/CPA, an oral contraceptive pill (OCP), can inhibit the hypothalamus and pituitary gland to decrease LH and androgen levels. Currently, studies have only reported that EE/CPA can improve biochemical hyperandrogenemia, acne, sebum, hirsuteness and other adverse clinical symptoms [10]. As early as 2004, researchers had proposed that the Diane/cetrorelix protocol has a similar pregnancy outcome to the GnRH agonist long protocol in PCOS; however, the drawback was the 3-month-long administration of EE/CPA [3]. Thus, OCPs can replace GnRH-a for downregulation and can reduce the side-effects [11]. In 2010, Tehraninejad *et al.* [12]. found that the agonist protocol after OCP pretreatment in patients with PCOS achieved similar clinical outcomes as the antagonist protocol triggered by GnRH, with a reduction in the incidence of OHSS. The present study compared the cycle characteristics and clinical efficiency of the EE/CPA downregulation with the standard GnRH-a long protocol in IVF/ICSI cycles.

The present study demonstrated that the oral administration of EE/CPA for downregulation in a COH regimen may be a better option for patients. First, it can be used at any time and flexible hours of the menstrual cycle, which provides great convenience for patients. Second, the number of oocytes retrieved, MII oocytes, fertilized oocytes, viable embryos and good-quality embryos were comparative to those of the control group. To a certain extent, the higher cleavage rate of EE/CPA group might reflect improved cytoplasmic maturation due to prolonged LH sup-

Table 3. Comparison of embryological outcomes of the two downregulation protocols.

Parameters	EE/CPA group (n = 392)	Control group (n = 392)	*p*-value
Gn dose (IU)	2920.80 ± 791.21	2745.40 ± 955.74	0.005
Gn duration (days)	11.11 ± 2.66	10.70 ± 2.55	0.028
Retrieved oocytes	14.67 ± 6.17	14.78 ± 5.60	0.809
MII oocyte	12.95 ± 5.82	13.24 ± 4.94	0.459
Fertilization			0.369
IVF	261 (66.6%)	249 (63.5%)	
ICSI	131 (33.4%)	143 (36.5%)	
Fertilized oocyte	11.59 ± 5.39	12.11 ± 4.80	0.154
Cleavage	11.36 ± 5.36	11.73 ± 4.72	0.309
Viable embryos	5.51 ± 2.98	5.96 ± 2.75	0.026
Good quality embryos	4.98 ± 2.90	5.19 ± 2.67	0.311
Mature oocyte rat	5078/5752 (88.3%)	5190/5792 (89.6%)	0.023
Fertilization rate	4541/5078 (89.5%)	4749/5190 (91.5%)	<0.001
Cleavage rate	4450/4541 (98.0%)	4597/4749 (96.8%)	<0.001
Viable embryo rate	2157/4541(47.5%)	2337/4749 (49.2%)	0.099
Good quality embryos rate	1953/4541 (43.0%)	2033/4749(42.8%)	0.846

Dates were expressed as the mean ± standard deviation or number (%).

Differences between the groups were analyzed by the Student's *t*-test or chi-squared test.

IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection; MII, meiosis stage II.

Table 4. Comparison of the costs of the drug downregulation protocols in the two groups.

Items	EE/CPA	Control	
		Short-acting GnRH-a	Long-acting GnRH-a
Drug	6.92–13.84	211.80	90.35–180.69
Gn	489.15–852.62	411.08–850.09	
FET		252.10	
Average	748.17–1118.56	874.98–1314.00	753.53–1282.88

GnRH, gonadotropin-releasing hormone; FET, frozen-thawed embryo transfer. Gn: $0.229 per unit; FET: $252.10 per cycle.

pression, minimizing premature luteinization of granulosa cells. A high cleavage rate is one of the main aims of such protocols for clinicians and patients. In addition, oral administration markedly alleviates the pain of intramuscular injections for the patients.

The study indicated that viable embryos were significantly fewer in the EE/CPA group, but good-quality embryo counts showed no difference. This phenomenon might be interpreted that the hyperandrogenic environment induced apoptosis of granulosa cells, leading to developmental arrest of the metaphase embryo. EE/CPA pretreatment significantly reduced serum free testosterone, and decreased the proportion of moderate-quality embryos, but there was no difference in the proportion of good-quality embryos. It suggested an elimination effect on low-potential embryos, which was related to the selective optimization of embryo development. Meanwhile, estrogen pretreatment enhanced oocyte maturation synchromia, and further optimized the distribution of embryo quality. Although the total number of viable embryos decreased, the retained good-quality embryos maintained the overall pregnancy potential, which was consistent with the non-inferior clinical outcome.

In addition, in the present study, Gn duration and total dose were comparable between groups, with adjustments made for individual ovarian response. The higher Gn requirement in the EE/CPA group may reflect prolonged pituitary suppression, necessitating higher doses to overcome follicular dormancy. This does not imply ovarian resistance, as oocyte yield remained comparable. The clinical pregnancy rate also did not differ significantly between the groups. Of note, the incidence of OHSS was significantly lower in the EE/CPA group compared to the control group. Thus, this suggests that the EE/CPA oral contraceptive may effectively inhibit the serum LH level, without affecting the clinical outcome.

With the impact of Corona Virus Disease (COVID)-19 in recent years, the economic capacity of individuals has also been greatly affected. The cost of IVF is becoming a matter of concern. Thus, clinicians aim to identify methods which may be used to achieve the most satisfactory results with the lowest costs. The cost of the use of EE/CPA is lower than that of conventional COH protocols. This is greatly appealing for patients.

With the development of vitrification, the survival rate of frozen-thawed embryos has markedly improved [13]. The oral administration of EE/CPA, which affects hormone levels, has negative effects on endometrial receptivity. Embryos obtained from the patients treated with EE/CPA thus require total freezing instead of fresh transfer. Therefore, the EE/CPA downregulation protocol can only be used with freeze-thaw embryo transfer. In the present study, freeze-thaw embryo transplantation was selected in all transplantation cycles. The clinical indicators demonstrated that there was no significant difference in the implantation and clinical pregnancy rates between the EE/CPA and control group. Above all, the use of EE/CPA markedly reduced the occurrence of severe OHSS. Perhaps EE/CPA can also help to reduce the adverse effects on endometrial receptivity in a high steroid environment [14], during the COH process, as well as when applying GnRH-a for ovarian stimulation.

Of note, the present study has several limitations which should be mentioned. First of all, a small percentage of patients experienced gastrointestinal adverse reactions following the administration of EE/CPA and they thus had to be administered other drugs for the downregulation protocol. Secondly, as of each patient responds differently to the drug, the dose of EE/CPA needs to be flexibly adjusted according to each individual. Thirdly, excessive downregulation may lead to an increase in the use of ovulation induction. Fourth, while embryologists were blinded, patients and clinicians were not blinded due to differing drug administration routes (oral vs. injection). This may introduce performance bias in subjective outcomes such as OHSS assessment. Finally, for the consistency, the study investigated the effect of EE/CPA down-regulation protocol on the clinical outcomes of IVF/FET cycles. The freeze-all protocol, while standardizing endometrial receptivity, may obscure potential advantages of GnRH-a in fresh transfers. Future studies should evaluate EE/CPA in fresh cycles and compare specific agonist regimens (short-acting and long-acting).

5. Conclusions

In the present study, the oral administration of EE/CPA as a downregulation protocol produced equivalent clinical outcomes compared with the control GnRH-a downregulation protocol. It may thus prove to be an effective strategy in ovarian stimulation protocols.

Availability of Data and Materials

The datasets generated during this study are available from the corresponding authors upon reasonable request.

Author Contributions

XB, FM and XW designed the research study. YW, SX and PZ collected materials and interpreted the patient data. XB and HW analyzed the data and wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was carried out in accordance with the guidelines of the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Children's Hospital of Shanxi and Women Health Center of Shanxi (approval number: IRB-KYYN-2021-00478). All patients or their families/legal guardians gave their informed consent for inclusion before they participated in the study.

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Conflict of Interest

The authors declare no conflict of interest.

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