Factors affecting pregnancy outcomes following the surgical removal of intrauterine adhesions and subsequent *in vitro* fertilization and embryo transfer

XUECHUN WANG[1], JINGSONG YI[1], XI XIE[1], SHENGRONG DU[2], LIYING LI[1] and XIUQIONG ZHENG[1]

[1]Department of Obstetrics and Gynecology, and [2]Assisted Reproductive Technologies Research Institute, Fujian Provincial Maternity and Children's Hospital, Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian 350001, P.R. China

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Abstract. This study aimed to investigate the clinical factors affecting pregnancy rates following the surgical removal of intrauterine adhesions (IUAs) and subsequent *in vitro* fertilization and embryo transfer (IVF-ET). We retrospectively evaluated case data from patients who had undergone hysteroscopic surgery to remove varying degrees of IUAs and who had subsequently received assisted reproductive treatments with IVF-ET (in all 140 cycles) at our hospital between January, 2011 and January, 2015. The patient data were divided into either the pregnancy or non-pregnancy groups based on the pregnancy outcomes, and a number of clinicopathological variables were compared these two groups, such as age, infertility (type and duration), the number of prior surgical treatments for and severity of IUAs, the baseline follicle-stimulating hormone/luteinizing hormone (FSH/LH) ratio and estradiol level, endometrial thickness on the day of human chorionic gonadotropin (hCG) administration, etc. We selected the variables with statistically significant differences to generate multivariate logistic regression and linear correlation analyses. We found that i) the mean endometrial thickness on the day of hCG administration was greater in the pregnancy group, and that the average gestational age was younger than that in the non-pregnancy group. The different age groups had significantly different pregnancy rates. The mean baseline FSH/LH ratio of the women in the pregnancy group was lower than that in the women in the non-pregnancy group. The number of embryos transferred in the pregnancy group was higher than that in the non-pregnancy group. However, the other variables exhibited similar values between these two groups. ii) Our multivariate logistic regression analyses revealed that age and endometrial thickness on the day of hCG administration had significant effects on the pregnancy outcome. The baseline FSH/LH ratio and the number of embryos transferred were similar between the groups. On the whole, age and endometrial thickness on the day of hCG administration are the most important predictors of pregnancy outcome in the patients undergoing IVF-ET following the surgical removal of IUAs. Importantly however, the identification of effective methods with which to improve the endometrial thickness and the ovarian response in patients with diminished ovarian reserves warrants further investigation in future research.

Correspondence to: Dr Jingsong Yi, Department of Obstetrics and Gynecology, Fujian Provincial Maternity and Children's Hospital, Affiliated Hospital of Fujian Medical University, 18 Daoshan Road, Gulou, Fuzhou, Fujian 350001, P.R. China
E-mail: yijingsong666@outlook.com

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Introduction

Intrauterine adhesions (IUAs) or Asherman syndrome (1) refers to the presence of fibrous bands in the endometrium of the uterus that result from damage due to physical or chemical factors, such as surgery or inflammatory diseases that destroy the lining of the intima and its normal self-repair capacity, causing the exudation and deposition of large amounts of fibrinogen. Adhesions between the inner walls of the uterus form where the walls abnormally adhere or stick to each other. IUAs lead to alterations in the uterine cavity size and shape, reductions in the normal endometrial area and changes in the uterine microenvironment (2). In addition, the endometrial receptivity is reduced, leading to infertility and to adverse effects on women's physical and mental health (3). Since the birth of a baby resulting from *in vitro* fertilization (IVF) in 1978, the rapid development of assisted reproductive technologies has brought joy to numerous otherwise infertile couples. Hysteroscopic surgery for the dissection of IUAs followed by reproductive assistance technology to aid conception is the most effective treatment for good pregnancy outcomes (4).

In this study, we examined cases of patients with IUAs from January, 2011 to January, 2015 at the Fujian Province Maternal and Child Health Hospital. These patients had been treated with hysteroscopic operations followed by assisted reproductive treatment for a total of 140 cycles, and the clinical factors affecting their pregnancy outcomes were identified.

Materials and methods

Patients. This Institutional Review Board approved study, analyzed cases from 140 cycles of assisted reproductive IVF-ET treatment from patients with varying degrees of IUAs who had undergone hysteroscopic surgery for the removal of IUAs at the Fujian Maternal and Child Health Hospital from January, 2011 to January, 2015. Informed written consent was obtained from all patients for the surgical procedures. For the present study, patient consent was waived as it was a retrospective analysis, with no direct contact between the authors and the patients, and personal privacy was protected through anonymization.

Data from 108 cycles of IVF and 32 cycles of intracytoplasmic single sperm injections (ICSIs). We included data from patient with ages ranging from 23 to 47 years with infertility durations ranging from 1 to 15 years. The causes of infertility varied (121 cases had secondary infertility and 19 had primary infertility), but included tubal infertility, partners with oligoasthenoteratozoospermia syndrome, repeated intrauterine insemination (IUI) failure, pelvic endometriosis IV, follicular rupture luteinization syndrome (LUFS), unexplained infertility and others. We included data from women with basal endocrine levels within the normal range and diagnosed as having varying degrees of IUAs; we also excluded data from patients with premature ovarian failure, space-occupying ovarian lesions, unilateral or bilateral hydrosalpinx, or endometritis prior to embryo transfers or uterine malformations.

Hysteroscopic surgery for the removal of IUAs. All patients underwent diagnostic hysteroscopy and treatment within 7 days following the clearance of their menstruation cycles. The physicians used hysteroscopy to determine the type and extent of the IUAs, and to place the micro-shear or vaporization electrode to separate the adhesions, and restore the shape and size of the uterine cavity to the greatest extent possible. Following the procedure, an intrauterine device (IUD) was placed into the uterus, followed by treatment with Bujiale® (estradiol valerate tablets) and dydrogesterone for 3 months. Finally, a hysteroscopy and IUD removal procedure were performed, and if deemed necessary, the IUA removal was repeated.

Classification of IUAs. Different classification systems for IUAs have been proposed according to the American Fertility Society (AFS) (5) as follows: i) According to the uterine area involvement: <1/3 (1 point), between 1/3 and 2/3 (2 points), >2/3 (4 points). ii) According to adhesion types: Filmy adhesion (1 point), filmy and dense (2 points), dense adhesion (4 points). iii) According to the menstrual pattern: Normal (0 points), hypomenorrhea (2 points) and amenorrhea (4 points). The summation of the scores from the three systems yields a final evaluation of the degree of IUAs (mild, 1-4 points; moderate, 5-8 points; and severe, 9-12 points).

IVF-ET method. Superovulation, egg retrieval, IVF, ICSI and embryo cultures were carried out following the routine procedures for assisted reproductive technology laboratories. On the third day of embryo culture, 1-2 embryos were selected for transfer. Following egg retrieval, the patients were injected progesterone to support the progress of the corpus luteum. Blood tests for human chorionic gonadotropin (hCG) were carried out 14 days after the embryo transfers. Patients with positive detection underwent ultrasonic tests after 5 weeks of implantation to observe the uterine cavity, the existence of gestational sacs and the fetal heartbeat as indicators of clinical pregnancy.

Embryo quality assessment. According to the evaluation standards presented in the study by Van Royen *et al* (6), the best blastomeres according to their morphology reach 8 cells on the third day following egg retrieval. High-quality embryos were defined as those being regularly uniform blastomeres with <20% fragmentation.

Grouping. Blood samples were obtained from patients for hCG tests 14 days following the embryo transfers. Biochemical pregnancies were identified by hCG levels >50 mIU/ml; ultrasound monitoring of the gestational sac and fetal heartbeat were performed 5 weeks following the embryo transfers to the uterine cavity. The data from the 140 cycles in the study were divided into a pregnancy and a non-pregnancy group according to the treatment outcome. The cases with clinical pregnancy formed the pregnancy group; while those without implantation, biochemical pregnancy, or ectopic pregnancy formed part of the non-pregnancy group. The following variables were compared between the two groups: Age, infertility duration, infertility type, number of prior surgical treatments for IUAs, IUA severity, number of prior uterine cavity operations, number of spontaneous abortions, baseline follicle-stimulating hormone/luteinizing hormone (FSH/LH) ratio, baseline estradiol level, body mass index, time interval between surgical treatment for IUAs and embryo transfer, endometrial thickness on the day of human chorionic gonadotropin administration, number of embryos transferred, and number of high-quality embryos transferred.

Statistical analyses. Statistical analyses were performed using 24.0 software (IBM, Inc.). Measurement data are expressed as the means ± standard deviation, and count data as numbers and percentages. Comparisons were made between groups using independent sample t-tests, and comparisons within groups using the Chi-squared test of listed data in tabulated row and column formats. Multivariate logistic regression and Pearson's correlation analyses were also conducted for the variables with significant differences following the t-test and the Chi-squared test. Values of $P<0.05$ were considered to indicate statistically significant differences.

Results

Association between clinical indicators and pregnancy outcomes in the two groups. Among the 140 cycles studied, we found 60 cases of clinical pregnancy (for a clinical pregnancy rate of 42.9%), and 80 cases of no implantation, biochemical pregnancy, or ectopic pregnancy. No significant differences were found in terms of infertility years, infertility type, the numbers of IUA procedures, the degree of the IUAs, the numbers of intrauterine surgeries, the number of spontaneous abortions, baseline estradiol values, body mass indexes, the

Table I. Comparison of clinical indicators in the groups with different pregnancy outcomes.

Clinical indicator	Pregnancy group (n=60)	Non-pregnancy group (n=80)	t/χ^2	P-value
Age (years)	31.68±4.35	33.65±5.12	-2.397	0.018[a]
<30	58.97% (23/39)	41.03% (16/39)	10.598	0.014[a]
30-35	40.82% (20/49)	59.18% (29/49)		
35-40	39.02% (16/41)	60.98% (25/41)		
≥0.	9.09% (1/11)	90.91% (10/11)		
Infertility duration (years)	4.85±3.22	4.35±3.04	0.938	0.350
Primary infertility	52.63% (10/19)	47.37% (9/19)	0.858	0.354
Secondary infertility	41.32% (50/121)	58.68% (71/121)		
Numbers of surgeries for intrauterine adhesion removal	1.30±0.63	1.58±1.15	-1.749	0.083
Intrauterine adhesions (mild)	41.54% (27/65)	58.46% (38/65)	1.163	0.559
Intrauterine adhesions (moderate)	43.14% (22/51)	56.86% (29/51)		
Intrauterine adhesions (severe)	54.17% (13/24)	45.83% (11/24)		
Number of intrauterine surgeries	1.16±1.19	1.27±1.15	-0.529	0.598
Number of spontaneous abortions	1.70±0.88	1.85±1.00	-0.590	0.558
Interval between intrauterine adhesion procedure (months)	9.89±5.68	12.18±7.84	-1.591	0.115
Basal FSH/LH	1.79±1.03	2.35±1.99	-1.996	0.048[a]
Basal estradiol (pg/ml)	69.86±114.67	55.15±58.25	0.909	0.366
body mass index (kg/m^2)	21.0±2.60	21.51±3.44	-0.759	0.450
Endometrial thickness (mm) on hCG trigger day	11.23±1.73	10.35±1.96	2.771	0.006[b]
Number of transferred embryos (one)	1.96±0.19	1.86±0.39	2.093	0.039[a]
Number of high-quality transferred embryos (one)	1.67±0.70	1.42±0.85	1.863	0.065

Data for age, infertility duration, numbers of surgeries for intrauterine adhesion removal, number of intrauterine surgeries, number of spontaneous abortions, interval between intrauterine adhesion procedure (months), basal FSH/LH levels, basal estradiol levels, body mass index, endometrial thickness, and the number of transferred embryos are presented as the means ± standard deviation. All other data are nominal and presented as percentages and numbers. [a]P<0.05; [b]P<0.01. FSH/LH, follicle-stimulating hormone/luteinizing hormone (FSH/LH); hCG, human chorionic gonadotropin.

Table II. multivariate logistic regression analysis of age, endometrial thickness on hCG the trigger day, basal FSH/LH level and the number of transferred embryos.

Index	Age	Transformation endometrial thickness	Basal FSH/LH	Number of transplanted embryos
B	-0.451	0.754	-0.262	0.962
Wald	4.404	7.121	0.811	1.765
OR value (95% confidence interval)	0.637 (0.418, 0.971)	2.125 (1.222, 3.697)	0.770 (0.435, 1.361)	2.617 (0.633, 10.822)
P-value	0.036[a]	0.008[b]	0.368	0.184

[a]P<0.05; [b]P<0.01. 'B' indicates the partial regression coefficient of the respective variables; FSH/LH, follicle-stimulating hormone/luteinizing hormone (FSH/LH); hCG, human chorionic gonadotropin.

interval between the IUA procedure and embryo transfer, and the numbers of transferred high-quality embryos (all P>0.05). The average endometrial thickness of the pregnancy group was higher than that of the non-pregnancy group, and the difference was statistically significant (t=2.771; P=0.006). In addition, the age difference (t=-2.397, P=0.018), the difference in basal FSH/LH levels (t=-1.996; P=0.048) and the difference in the number of transferred embryos (t=2.093, P=0.039<0.05) between the two groups were all statistically significant (Table I).

Multivariate logistic regression analysis of age, transformation endometrial thickness, basal FSH/LH levels and the number of transferred embryos. We performed multivariate logistic regression analyses for age, transformation day endometrial thickness, basal FSH/LH levels and the number

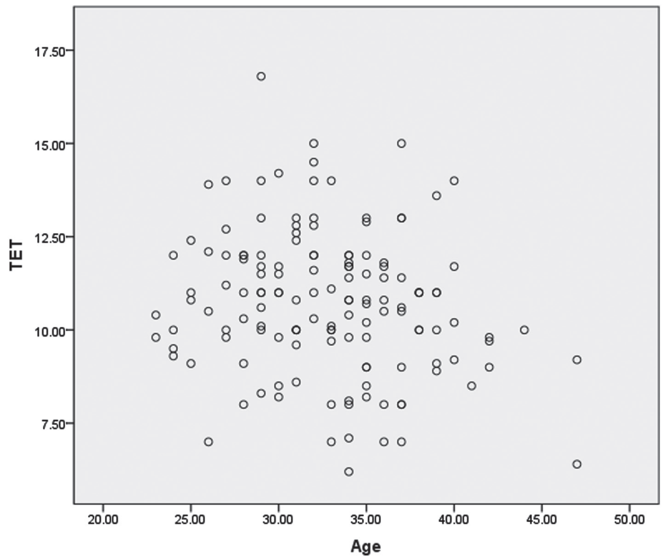

Figure 1. Pearson's correlation analysis between age and endometrial thickness on the day of endometrial secretory transformation.

of transferred embryos. The results indicated that the age (OR, 0.637; 95% CI, 0.418-0.971; P<0.05) and endometrial thickness on the day of endometrial secretory transformation (OR, 2.125; 95% CI, 1.222-3.697; P<0.01) significantly affected the pregnancy outcomes. We found that the basal FSH/LH level and the number of transferred embryos did not differ significantly (P>0.05) affect pregnancy outcomes according to our multivariate logistic regression analysis (Table II).

Correlation analysis of age and endometrial thickness on the day of triple layer appearance. We assessed the correlation between age and endometrial thickness on the day of triple layer appearance using Pearson's correlation analysis. Our analysis indicated no correlation between age and endometrial thickness (r=-0.185, P=0.029) (Fig. 1).

Discussion

Occurrence, prevention and treatment of IUAs. IUAs can be caused by trauma, infection, or low estrogen levels (7). A history of dilation and curettage (D&C) is an important risk factor for IUAs. Intrauterine infections are also an important cause of IUAs (8). IUAs can also occur in patients with non-tuberculous endometritis and lacking a history of intrauterine surgery; in fact, Lim *et al* demonstrated that postpartum or post-surgical low estrogen levels affected the repair of the endometrium, leading to IUAs (9). Thus, the endometrium post-pregnancy is more vulnerable, accounting for approximately 90% of all IUAs, most often following natural childbirth, cesarean section, or abortion. In this study, we examined 121 cases of secondary infertility (86.4%), and only 19 cases of primary infertility (13.6%), suggesting that secondary infertility causes IUAs more often, in agreement with the findings of the previous study mentioned (9).

The treatment of IUAs involves the accurate and thorough separation of adhesions, the prevention of post-operative re-adhesions and the promotion of endometrial hyperplasia (10,11). The current comprehensive treatment is mainly based on surgical adhesion removal. Surgical treatment not only restores the normal shape of the uterine cavity, but also improves the blood supply to its tissues, preventing re-adhesions. In addition, the comprehensive treatment utilizes estradiol valerate and dydrogesterone to promote endometrial repair and restore its normal function. Experts at home and abroad have recognized that hysteroscopic separation of adhesions is the 'golden' method for the treatment of IUAs (3). An advantage of the treatment is that the remodeling of the uterine cavity shape relieves the binding to the sub-endothelium muscle layer, restores the normal peristaltic function, increases the blood supply of the endometrial tissue, and facilitates the regeneration of endometrial epithelial cells that accelerates damage repairs. The formation of physical barriers helps prevent re-adhesion, and drug-promoted endometrial hyperplasia promotes the repair into a fully functional uterus. In this study, through hysteroscopic surgery, the patients in all 140 cycles recovered with a normal intrauterine morphology, and endometrial growth was promoted by supplying the patients with post-operative estrogen supplementation. Overall, we observed marked improvements in all the patients.

Preventing unintended pregnancies to avoid abortions, and if necessary, improving the D&C technique to make it safer will be key to reducing the incidence of complications, such as IUAs, and to improve successful pregnancy rates. The accurate and complete treatment of IUAs is important in order to re-establish normal menstruations and to improve pregnancy outcomes. Thus far, no effective method for the prevention of IUAs exists, at least to the best of our knowledge. The endometrium lining is typically non-renewable, and if the basal layer is severely traumatized, IUAs are unavoidable, and the probability of re-adhesions following uterine adhesion removal is high. The key for the fundamental prevention of IUAs is to minimize 'avoidable' uterine operations particularly abortions.

Effects of age and ovarian functional status on pregnancy outcome following IVF-ET. A number of women tend to wait a long time before attempting to have their first child, and with the opening of the second child policy in China, older-aged women are again having fertility needs. Age is associated with the female reproductive capacity (12), and the number of patients with diminished ovarian reserves (DORs) has increased. The ovarian reserve reflects the reproductive potential left within a woman's two ovaries; the ability of the ovarian cortex to form fertile oocytes is mainly determined by the number and quality of the antral follicles in that ovary (13). Due to the smaller number of oocytes available to patients with DORs, the number of embryos that can be obtained is lower, the cycle cancellation rate is higher, and the clinical pregnancy rate is lower than that in patients without DORs (14). This has been a difficult problem to solve during IVF-ET treatment cycles (15). Fernandez *et al* (16) and others have demonstrated that the post-operative pregnancy rates of patients with IUAs are 23.5% in the >35-year-old group and 66.6% in the <35-year-old group; in addition, the live birth rates have been shown to be 14.7 and 53.5%, respectively, with the difference being statistically significant. A patient with a diminished ovarian reserve has an increased basal serum FSH/LH ratio, and this ratio is a good predictor of ovarian function (17). In this study, the ratio of FSH/LH in the non-pregnancy group (2.35±1.99) was higher than that in the pregnancy group (1.79±1.03), and the difference was statistically significant (t=-1.996; P=0.048); however, our multivariate logistic regression analysis revealed that the difference was not statistically significant (P>0.05), probably due to the small sample size in this study.

We found that the mean age of the women in the non-pregnancy group (33.65±5.12) was higher than that of women in the pregnancy group (31.68±4.35), with a statistically significant difference (t=-2.397; P=0.018). With increases in age, the clinical pregnancy rate decreased significantly. Moreover, our multivariate logistic regression analysis revealed that age had a significant effect on pregnancy outcome, and our results suggest that age is the main predictor of clinical pregnancy.

Improving the pregnancy outcome of patients with DORs is a goal of many researchers. Weall *et al* have demonstrated that the use of growth hormone (GH) during the ovulation induction process can improve the ovarian response, the clinical pregnancy rate and the live birth rate of patients with DORs (18). IVF treatment together with androgen administration or a modulator in patients with DORs can improve the clinical pregnancy rate, reduce the total amount of GH used, and improve the pregnancy outcome (19). However, due to the lack of large-scale control studies, these results remain controversial. Future large-scale randomized controlled trials are required to obtain more convincing conclusions.

Effect of endometrial thickness on the outcome of IVF-ET pregnancy. The ability of the endometrium to allow blastocyst positioning, adhesion and implantation is known as endometrial receptivity, and is one of the main factors influencing the pregnancy outcome. The thickness of the intima must reach a certain threshold to be receptive, that is, an endometrium above a certain thickness is a pre-requisite condition for embryo implantation, and thinning of the intima is an important cause of low implantation rates. An appropriate uterine thickness can increase the clinical pregnancy rate (20). The endometrial thickness during the transfer window for the embryo is a predictor of the embryo implantation outcome (21). Clinically, the thickness of the endometrium on the hCG 'trigger day' (or progesterone conversion 'trigger day') is regarded as an appropriate evaluation of the endometrium embryo reception adequacy (22). Clinical studies have shown that if the endometrial thickness is ≤7 mm, the clinical pregnancy probability is significantly reduced (20). In this study, the mean endometrial thickness in the pregnancy group was 11.23±1.73 mm, higher than that in the non-pregnancy group (10.35±1.96 mm), and the difference between the two groups was statistically significant (t=2.771; P=0.006). Our logistic regression analysis revealed that the endometrial thickness on the hCG trigger day had a significant effect on the pregnancy outcome (OR, 2.125; 95% CI, 1.222-3.697; P<0.01). Our analysis of the correlation between age and endometrial thickness on the hCG trigger day revealed no significant correlation (r=-0.185; P=0.029). On the other hand, Gonen *et al* have reported that the endometrial thickness on the hCG trigger day correlates with age, and has predictive value for pregnancy outcomes (23).

The recovery of uterine cavity morphology is a basic requirement of the treatment of IUAs, and the improvement of endometrial receptivity is equally important. The improvement of endometrial thickness is the most direct and effective means with which to improve clinical pregnancy rates. Measures to this effect include traditional hormone therapy (24), vasoactive drug therapy (25), and regenerative medicine (26). However, a small number of patients with thin endometria remain difficult to treat, and innovative and effective treatment methods are still being actively explored.

Effect of number of transferred embryos on pregnancy: Outcome of IVF-ET. A major challenge in the field of assisted reproduction has been identifying methods with which to reduce the rate of multiple pregnancies due to the high clinical pregnancy rate of IVF-ET. Huang *et al* studied the IVF-ET treatment cycles of women aged 35-36 years, comparing cycles after transferring 3 embryos with those after transferring 2 embryos, and found that the difference in the clinical pregnancy rate was not statistically significant, although the multiple pregnancy incidences increased significantly (27). Luo *et al* concluded that in order to ensure a clinical pregnancy and reduce the incidence of multiple pregnancies, transferring 3 embryos is optimal in women >38 years of age or in those between 35 and 37 years of age without high-quality embryos (28). For women <38 years of age with high-quality embryos, the number of transferred embryos should be reduced from 3 to 2, and the remaining embryos can be cryopreserved, to avoid embryo waste and reduce the multiple pregnancy incidence. In this study, the number of embryos transferred in the pregnancy group (1.96±0.19) was higher than that in the non-pregnancy group (1.86±0.39), and the difference was statistically significant (t=2.093; P=0.039); however, our multivariate logistic regression analysis revealed no statistically significant differences (P>0.05).

In the presence of an appropriate endometrial condition, the number of embryos to transfer can be determined jointly by the doctor and the patient. The decision affects not only the pregnancy outcome, but also the mother-child and postpartum health. In recent years, single embryo transfers have become the focus of many assisted reproductive centers worldwide to ensure safe outcomes (29).

In conclusion, for patients undergoing IVF-ET treatment following the surgical removal of IUAs, age and endometrial thickness on the day of triple layer appearance are the most important predictors of pregnancy outcomes. Future studies are required however, to focus on identifying methods with which to effectively improve endometrial thickness and ovarian response in patients with a diminished ovarian reserve in order to improve pregnancy rates and outcomes.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XW was involved in the conception and design of the study and in data collection, and in the writing of the manuscript.

JY was involved in the conception and design of the study and in the editing of the manuscript. XX was involved in the data interpretation and editing of the manuscript. SD and LL were involved in data collection. XZ was involved in data collection. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The Ethics Committee of the Fujian Provincial Maternity and Children's Hospital approved this retrospective medical record review (approval no. 20192006). Informed written consent was obtained from all patients for the surgical procedures. For the present study, patient consent was waived as it was a retrospective analysis, with no direct contact between the authors and the patients, and personal privacy was protected through anonymization.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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