Archives of Gynecology and Obstetrics (2019) 300:933–939
https://doi.org/10.1007/s00404-019-05249-y

GENERAL GYNECOLOGY

Estrogen therapy before hysteroscopic adhesiolysis improves the fertility outcome in patients with intrauterine adhesions

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Received: 5 April 2019 / Accepted: 10 July 2019 / Published online: 26 July 2019

Abstract

Purposes To describe the fertility outcomes after hysteroscopic adhesiolysis combined with preoperative hormone treatment in women with intrauterine adhesion (IUA).

Methods This study is a retrospective cohort study. A total of 230 patients with IUA underwent hysteroscopic adhesiolysis combined with hormone treatment from Jan 2012 to Jun 2018. 148 patients who received preoperative estrogen treatment were enrolled into group A and 82 patients without preoperative estrogen treatment were enrolled into group B. All the patients underwent hysteroscopic adhesiolysis and received postoperative estrogen therapy, intrauterine indwelling device. Second or third look was performed after 2–3 months.

Results 90.87% (209/230) patients complete the study. The AFS scores at baseline were higher in the group A than group B. After the preoperative E2 treatment, group A achieved the comparable AFS score to group B before the surgery. The cumulative fertility rate in group A was comparable in group B, both in the ITT analysis (49.32% vs. 52.44%, $p=0.651$) and the PP analysis (54.07% vs.58.10%, $p=0.575$).The mean conception time was also similar in group A and group B (8.30 ± 6.47 vs. 8.54 ± 5.68 months, $p=0.837$). Besides, the surgery times in group A were less than group B. There was no difference in the rate of adverse events between two groups.

Conclusions Hysteroscopic adhesiolysis combined with preoperative oestrogen could reduce the preoperative AFS scores and the times of surgery which yield a similar conception rate in women with less severe intrauterine adhesions.

Keywords Intrauterine adhesions · Hysteroscopic adhesiolysis · Estrogen therapy · Conception

Introduction

Intrauterine adhesions are caused by trauma of the basal layer of the endometrium, and associated with menstrual disorders, recurrence miscarriage, and infertility [1, 2]. Although the true prevalence of intrauterine adhesions is difficult to establish for a large number of patients having no symptoms [3], the prevalence of intrauterine adhesions was up to 19.1% after a first trimester miscarriage [4] and 21.5% in women with a history of postpartum curettage [5]. With the improvement of imaging modalities and widespread use of hysteroscopy, the diagnostic rates of IUAs is increasing [6].

The treatment modality of IUAs is based on symptoms such as hypomenorrhea or amenorrhea, pain, or, more commonly, infertility or recurrent pregnancy loss [7, 8]. Secondary infertility as an initial symptom has been reported in as high as 43% of women with intrauterine adhesions [2]. In these patients, the ultimate goal of surgery is to restore the function of uterine cavity physiologically and surgery still remains the main therapy [5]. Many preoperative, intraoperative, and postoperative measures have been described to improve surgical outcomes, including endometrial proliferation with estrogen (E2),

Luping Zhang and Ming Wang are equal first author contribution.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00404-019-05249-y) contains supplementary material, which is available to authorized users.

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hysteroscopic adhesiolysis under ultrasound surveillance, and mechanical separation of the endometrium [9–12]. In previous studies, the women treated with traditional various adhesiolysis could achieve 38.9% term delivery [13]. After combination of hysteroscopic adhesiolysis and intrauterine balloon or copper IUD, the live birth rate ranges from 16 to 41% and the difference may be attributed to different follow-up period [14, 15]. Postoperative oestrogen therapy has been widely used by many investigators to prevent recurrence of the adhesions [15, 16]. Previous study has suggested that ultrasound-directed hysteroscopic lysis combined prolonged preoperative and postoperative oral E2 provides the best possible outcomes in poor-prognosis women with severe Asherman syndrome [9]. However, the existing studies regarding the efficacy and safety of hysteroscopic lysis combined preoperative oral E2 of low quality for the small sample size and no control group.

Because few data are available regarding fertility outcomes after hysteroscopic adhesiolysis combined with preoperative hormone treatment in women with IUA [17]. Furthermore, there is a lack of evidence for comparing the efficacy of hysteroscopic adhesiolysis combined prolonged preoperative and postoperative oral E2 with the hysteroscopic adhesiolysis combined prolonged postoperative oral E2. Therefore, we conducted a retrospective study of 230 patients to depict a more complete picture of the real-world clinical pregnancy rates and to verify the efficacy and safety of hysteroscopic adhesiolysis combined prolonged preoperative and postoperative oral E2.

Materials and methods

This is a retrospective, open-label, cohort study in which patients were recruited from a tertiary care hospital, the Beijing Tiantan Hospital in China between Jan 2012 and Jun 2018. This study was approved by the institutional ethics review committee (KY 2018-105-04). IUA subjects were screened for the following eligibility criteria: age between 20 and 45 years; patients with the diagnosis of IUA (verified with hysteroscopy), and received hysteroscopic adhesiolysis and estrogen treatment. Key exclusion criteria included previous history of uterine artery embolization, primary infertility; evidence of endometriosis, tuberculosis, endometrial dysplasia, and abnormal semen in spouse; with the need of contraception (Fig. 1). Women fulfilling the inclusion and exclusion criteria were enrolled in the study. Demographic and baseline clinical data were abstracted from the clinical records. A total of 230 patients with IUA underwent hysteroscopic adhesiolysis combined with hormone treatment from Jan 2012 to Jun 2018. 148 patients who received preoperative estrogen treatment were enrolled into group A and 82 patients who had not received preoperative estrogen treatment were enrolled into group B. All the patients underwent hysteroscopic adhesiolysis and received postoperative

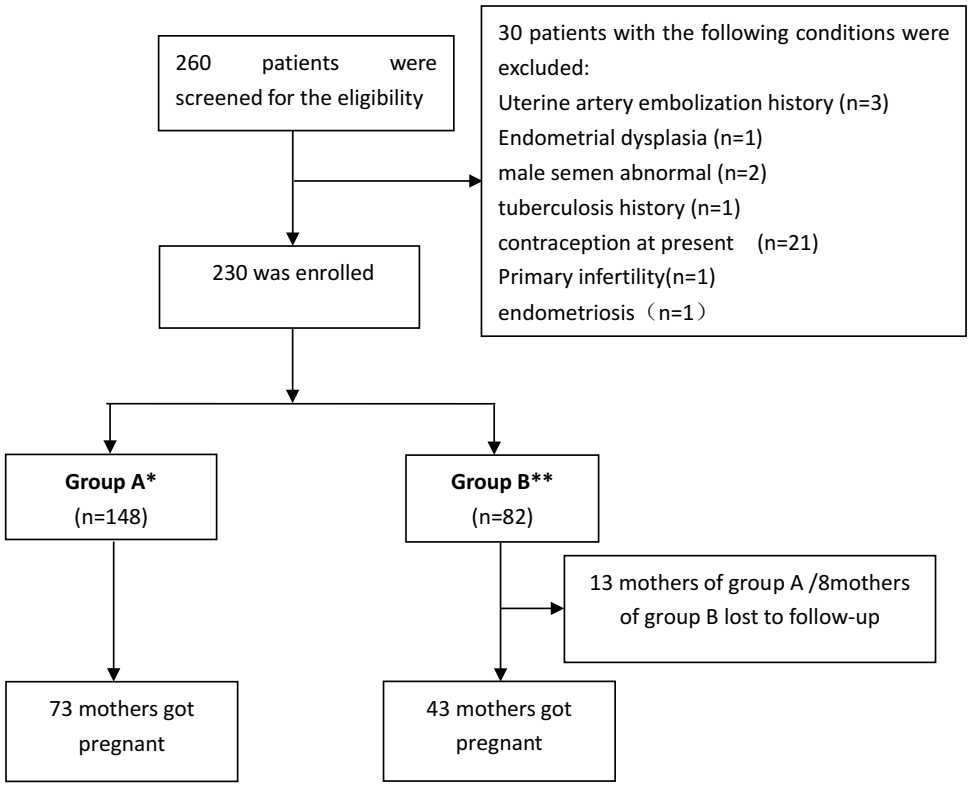

Fig. 1 Patients' selections and study design. Flowchart of the women who participated in the study of estrogen therapy before hysteroscopic adhesiolysis improves the fertility outcome in patients with intrauterine adhesions. *IUD* intrauterine device. *Group A: Preoperative estrogen treatment, hysteroscopic lysis, and postoperative estrogen treatment associated with IUD. **Group B: Hysteroscopic lysis and postoperative estrogen treatment associated with IUD

estrogen therapy, intrauterine indwelling device. Second or third look was performed after 2–3 months.

The patients received an office hysteroscopy to assess the uterine anatomy and confirm the AFS score under general anaesthesia, through a 4.5 mm-diameter hysteroscope without prior cervical dilatation and 5% glucose solution as the distending medium. The distension pressure was set at 100 mmHg. The types of IUA were classified according to the AFS scoring system (AFS 1988 version) system [18]. The patients in group A who were administrated hormone therapy consisting of estradiol valerate (Progynova, Bayer, Germany) at a dose of 6–8 mg daily for 8 weeks before hysteroscopic adhesiolysis, with the addition of dydrogesterone (Duphaston, Abbott, USA) at a dose of 10 mg daily in the last 10 days of oestrogen treatment. The patients in group B without preoperative estrogen treatment received hysteroscopic adhesiolysis directly. Hysteroscopic adhesiolysis was performed under simultaneous transabdominal ultrasound surveillance to help directed the hysteroscopic lysis. The Lamiken-R dilator was used for cervical ripening 2–4 h before surgery, which could facilitate cervical dilatation. The procedure was conducted under general anesthesia. A 12°resectoscope with an outer sheath diameter of 8.5 mm (Olympus, Japan) was then introduced into the uterine cavity. 5% glucose solution was used as the distension medium, at a pressure of 100–120 mmHg. A monopole loop or needle electrode was used to divide the adhesions, with cutting power set at 30 w. The procedures were performed by one of the two experienced endoscopic surgeons. The occurrence of any complications was recorded. All patients received hormone therapy postoperation consisting of estradiol valerate at a dose of 6–8 mg daily for 8 weeks, with the addition of dydrogesterone in the last 10 days of oestrogen treatment. A second-look hysteroscopy was carried out in the early proliferative phase 2–3 months after initial surgery. Following assessment of the extent and severity of any reformed adhesions, hysteroscopic adhesiolysis was also performed for patients with recurrence of adhesion at the second-look procedure. Hysteroscopic surgery continued until a normal uterine shape was achieved.

Demographic and baseline clinical data were extracted from the electronic clinical records. Characteristics of the hysteroscopic were registered postoperatively and we can collected from the electronic clinical records. A telephone follow-up was used to collect fertility data, with women asked to recall their pregnancy way and time, delivery way and delivery gestational age, perinatal complications, and neonatal data.

Our primary outcomes were the cumulative rate of conception and the fertility profiles after hysteroscopic lysis combined hormone treatment. The second outcomes were the conception time, operation time, changing of AFS scores, and adverse events of hormone treatment. The fertility profiles assessment include pregnancy rate, miscarriage rate, preterm rate, as well as live birth rate between different protocols.

Based on the studies by Myers et al. and Orhue et al. [9], we estimated 67% of patients with ultrasound-directed hysteroscopic lysis combined prolonged preoperative and 31% of patients with the ultrasound-directed hysteroscopic lysis combined prolonged postoperative oral E2 conceived, and the number of patients needed was calculated to be 39, with a significance level of 0.05 (one-tailed) and detection power of 0.90. Considering a 10% drop-outs rate, a sample size of patient enrolment more than 43 was a reasonable estimation for each group. Baseline characteristics and laboratory results were summarized for the comparative groups by means of descriptive statistics, including percentage, means ± standard deviation (SD), and 95% CI. For the quantitative variable, the *t* test was used to compare group differences. Chi-square test was used for categorical variables, and Mann–Whitney *U* test was used for multiple comparisons. Kaplan–Meier method was used to construct cumulative conception rate curves, and statistical significance between the curves was compared with log-rank tests. For endpoint measurements, we performed the protocol analysis, which was defined as analysis included all enrolled patients, including those with protocol deviations. However, patients who were lost to follow-up or who discontinued the study for any other reason(s) were excluded. In addition, we performed ITT analysis of the rates of pregnancy, and we included all enrolled patients. Significance level was set at $p < 0.05$; all data were analyzed by SPSS 23.0 (SPSS, IBM., NYU).

Results

Among 260 patients screened, 230 patients were enrolled in the study. 30 of them were excluded from the study for the following reasons: 3 women had the history of uterine artery embolism, 1 women with endometrial dysplasia, 2 women had abnormal semen examination in their husband, 1 women had the history of tuberculosis, 21 women did not wish to conceive after their operation, 1 women was primary infertility, and 1 women was endometriosis. 21subjects were lost to follow-up after the treatment, which included13 patients in group A before conception and 8 in group B. The disposition of our study patients is shown in Fig. 1. Baseline characteristics of the two study arms were similar besides the AFS scores before E2 therapy and are shown in Table 1. At baseline, the AFS scores of group A were significantly higher in group A than in group B (9.81 ± 1.79 vs.7.95 ± 2.56, $p < 0.05$). The mean (± SD) time of follow-up was 32.36 (SD 19.51) and 36.99 (SD 20.02) months for patients in group A and group B, respectively. The mean (± SD)

Table 1 Baseline characteristics of patients with intrauterine adhesion ($n=230$)

Median (range)	Group A ($n=148$)	Group B ($n=82$)	p value
Age at the time of diagnosis (years) (mean ± SD)	31.07 ± 4.74	31.61 ± 4.64	$t=0.827$, $p=0.409$[a]
Gravidity (mean ± SD)	2.41 ± 1.56	2.67 ± 1.76	$t=1.179$, $p=0.240$[a]
Parity (mean ± SD)	0.28 ± 0.52	0.34 ± 0.53	$t=0.897$, $p=0.371$[a]
Menstrual model			
Hypomenorrhea	104	62	$\chi^2=0.749$, $p=0.387$[b]
Amenorrhea	44	20	
AFS scores preoperative (mean ± SD)	9.81 ± 1.79	7.95 ± 2.56	$t=5.834$, $p=4.33E{-}8<0.05$[a]
IUA grade based on AFS scores			
Mild	2	6	$Z=5.853$, $p=4.83E{-}9<0.05$[c]
Moderate	33	45	
Severe	113	31	
History of past pregnancy (mean ± SD)			
Spontaneous abortion	0.11 ± 0.40	0.21 ± 0.56	$t=1.457$, $p=0.147$[a]
Missed abortion	0.76 ± 1.19	0.59 ± 0.89	$t=1.183$, $p=0.238$[a]
Artificial abortion	1.04 ± 1.24	1.24 ± 1.48	$t=1.111$, $p=0.268$[a]
Medical abortion	0.08 ± 0.30	0.09 ± 0.32	$t=0.102$, $p=0.919$[a]
Induced abortion	0.08 ± 0.30	0.07 ± 0.26	$t=0.201$, $p=0.841$[a]
Ectopic pregnancy	0.05 ± 0.21	0.98 ± 0.30	$t=1.479$, $p=0.140$[a]
Curettage	0.20 ± 0.53	0.27 ± 0.52	$t=0.996$, $p=0.320$[a]

IUA intrauterine adhesion, *AFS Score* the cumulative scores of the classification of the American Fertility Society (AFS)

[a]Independent samples *t* test

[b]Chi-square test

[c]Mann–Whitney *U* test

dosages and duration of preoperative E2 therapy before the first hysteroscopic adhesiolysis were 7.035 ± 1.002 mg and 7.818 ± 0.924 weeks.

After the preoperative E2 treatment, group A had a mean AFS score decline > 1 score, resulting in a comparable AFS score to group B (8.59 ± 2.31 vs.7.98 ± 2.54, $p=0.053$). In group A, 6.58% women (10/152) conceived after IVF treatment, 0.66% women (1/152) conceived after stimulate ovulation, and all other women (62/152) conceived spontaneously. In group B, 2.38% women (2/84) conceived after IVF treatment, 3.57% women (3/84) conceived after stimulate ovulation, and all other women (38/84) conceived spontaneously.

At the time of analysis, patients in group A had a cumulative conception rate of 59.3% and was comparable to patients in group B with 65.7% ($p=0.482$) (supplement Fig. 1). According to ITT analysis, 49.32% [73 of 148] of patients in group A got pregnant, compared to 52.44% [43 of 82] in group B ($p=0.651$). The mean conception time was similar in group A and group B (8.30 ± 6.47 vs. 8.54 ± 5.68 months, $p=0.837$). In group A, the median interval between surgery and pregnancy was 8.30 ± 6.47 months. 10 pregnancies were miscarriage, 3 patients were ectopic pregnancy, and 12 pregnancies were ongoing, 48 pregnancies processed into the third trimester, and 48 pregnancies achieved live birth, while 4 had preterm deliveries after pregnant. In group B, the median interval between surgery and pregnancy was 8.54 ± 5.68 months. 8 pregnancies were miscarriage, 9 pregnancies were ongoing, 27 pregnancies processed into the third trimester, and 27 pregnancies achieved live birth, while 1 had preterm deliveries after pregnant (Table 2).

To explore the benefits of estradiol treatment before hysteroscopic adhesiolysis in IUA patients with different ages and severities, we compared the conception rate in both groups after adjusting the ages and IUA severities, respectively. Also, there was no difference in conception rate according to the severity of IUAs (supplement Table 1) and ages younger or older than 35 years old.

The operation times was significantly shorter in group A than in group B (1.40 ± 0.67 vs. 1.69 ± 0.71, $p=0.003$) (supplement Table 2). Treatment with preoperative estrogen and hysteroscopic adhesiolysis was generally well tolerated by patients. During the treatment period, there were five itemized AEs recorded based on the patients' complaints, physical findings, and laboratory abnormalities, which included breast pain, nauseated, headache, transiently abnormal liver function, and TURP syndrome (supplement Table 3). All AEs reported were grade I–II except one TURP syndromes in each group, respectively, during the first hysteroscopic adhesiolysis. After targeting treatment, the symptoms

Table 2 The fertility profiles and menstrual patterns outcomes of the two groups

N (%)	Group A	Group B	t/χ^2 *p* value
Conception rate			
Conception rate—PP	73/135	43/74	$\chi^2=0.315$, $p=0.575$[a]
Conception rate—ITT	73/148	43/82	$\chi^2=0.205$, $p=0.651$[a]
Reproductive profile	135	74	
Miscarriage	10	8	$\chi^2=0.703$, $p=0.402$[a]
Ectopic pregnancy-per protocol	3	0	Fisher's test, $p=0.554$[b]
Preterm	4	1	Fisher's test, $p=0.658$[b]
Live birth	44	26	$\chi^2=0.139$, $p=0.710$[a]
Ongoing-per protocol	12	9	$\chi^2=0.567$, $p=0.452$[a]
The proportions of retrieve normal menstrual patterns			
Normal menses—PP	77/135	40/74	$\chi^2=0.173$, $p=0.678$[a]
Normal menses—ITT	77/148	40/82	$\chi^2=0.223$, $p=0.637$[a]

PP per-protocol analysis, *ITT* intention-to-treat analysis

[a]$\chi 2$ test

[b]Fisher's exact test

relieved quickly in both patients. No other severe AEs observed in this study.

Discussion

In this study, we report the fertility outcome of a retrospective cohort study on two different protocol for IUA patients whether combined estrogen therapy or not before hysteroscopic adhesiolysis. Estrogen therapy has been widely used prevent the adhesion reformation after hysteroscopic adhesiolysis [17], and was recommend as Grade B evidence [19]. Some studies used oestrogen therapy to prevent the adhesion recurrence [15] or improve the conception rate [9] in patients with severe and moderate IUA. However, the existing studies regarding the efficacy and safety of estradiol treatment before hysteroscopic lysis were of low quality for the small sample size and lack of control groups.

Myers, et al. described a retrospective case series of 12 patients to evaluate the effect on resumption of menses, pregnancy, and delivery with comprehensive management, which combined administration of prolonged preoperative, postoperative oral E2, intraoperative abdominal ultrasound-directed hysteroscopic lysis of uterine synechiae, postoperative placement of intrauterine device, and mechanically lyse newly formed adhesions during follow-up. All women resumed menses with follow-up ranging from 6 months to 10 years and 6 of 9 women less than age 39 years (67%) became pregnant, and four of six achieved a term or near-term delivery [9]. In our study, we analyzed the operation information and fertility results about preoperative oestrogen therapy in IUA patients. There was no difference in the baseline characteristics between two groups except the AFS scores at the first visit. Patients in group A had a higher AFS scores than group B (9.81 ± 1.79 vs. 7.95 ± 2.56, $p<0.05$), which indicated a more severe degree of IUA. After E2 treatment, AFS scores of group A were comparable to group B before hysteroscopic adhesiolysis. After the surgery, patients in group A achieved a similar cumulative conception rate to group B, both in the intention-to-treat analysis [with fertility rate of 49.32% (73 of 148) vs. 52.44% (43 of 82), $p=0.651$] and the per-protocol analysis (with fertility rate of 54.07% (73 of 135) vs.58.10% (43 of 74), $p=0.575$]. The overall conception rate was similar to earlier reports [20, 21]. The mean conception time was also similar in group A and group B (8.30 ± 6.47 vs. 8.54 ± 5.68 months, $p=0.837$). To explore the benefits of estradiol treatment before hysteroscopic adhesiolysis in IUA patients with different severities and ages, we compared the conception rate in both group after adjusting the IUA severities and ages, respectively. In addition, there was no difference in conception rate according to the severity of IUAs (supplement Table 1) and ages younger or older than 35 years old. Thomson et al. [22] used high-dose conjugated estrogen 2.5 mg postoperative showed that the conception rates were 43% and 57% in those with moderate adhesions. Yu et al. [20] and Chen et al. [21] used of 4 mg estradiol valerate after the hysteroscopic adhesiolysis which showed that the conception rates were 43% and 53.4% in those with moderate adhesions, and 32.5% and 25% in those with severe adhesions. The conception rate of moderate and severe IUA patients is higher or similar than the earlier reports in our study. At the time of analysis, 48 pregnancies of group A processed into the third trimester, 48 pregnancies achieved live birth, and 12 pregnancies were ongoing. In

group B, 27 pregnancies processed into the third trimester, 27 pregnancies achieved live birth, and 9 pregnancies were ongoing. The fertility outcome profiles were similar in two groups ($Z=0.519$, $p=0.604$).Our data, together with Myers study, further support the use of preoperative E2 before surgery in infertility patients with IUAs.

In term of safety data, we identified that more than 7% of patients experienced the following AEs: breast swelling pain, nausea, headache, transiently abnormal liver function, and TURP syndromes. All AEs reported were grades I–II except one TURP syndrome in each group, respectively, during the first hysteroscopic adhesiolysis, which was considered to be related with the time of adhesiolysis. In our study, the operation times was significantly shorter in group A than in group B (1.40 ± 0.67 vs. $1.69 \pm 0.711.73 \pm 0.96$, $p=0.003$). However, there was no significant difference of its occurrence between two groups. After targeting treatment, the symptoms relieved quickly in both patients. No other severe AEs observed in this study.

Our trial provides the largest cohort examining the safety and efficacy of hysteroscopic adhesiolysis combined with preoperative estrogen in patients with IUAs. However, the sample size between two groups was not equal in our study, which may reduce our efficiency but not change the statistical speculation. According to the previous literature, we calculate the least sample size to be 44 for each group, which was smaller than our fewer groups. To simulated a real-life setting and reduce the statistical error, we listed all the cases instead match group B with patients of group A. Besides, our study did not include treatment-experienced patients for too much confounding factors. Thus, our results may not be generalizable to patients with previous history. It may also be a limitation that it is a retrospective cohort study; a prospective study can be performed in the future. However, even with the several approaches for severe intrauterine adhesion, the result was still frustrated by low conception rates. To understand the molecular mechanisms behind IUA, increase the number of endometrial stem cells and improve the micro-environment of endometrial cell growth will open avenues to innovative therapy.

In conclusion, our results indicated that hysteroscopic adhesiolysis combined with preoperative oestrogen could reduce the AFS scores, decrease the times of surgery, and improve the fertility rate in women with moderate-to-severe intrauterine adhesions.

Author contributions LZ: project development, study design, data management and analysis, and manuscript writing. MW: project development, study design, data management and analysis, and manuscript writing. LZ and MW are equal first author contribution status. QZ: data collection. WZ: provided clinical expertise and supervision, and data collection. BY: provided clinical expertise and supervision, and data collection. HS: data collection. XS: data collection. YM: data collection. BW: data collection. LF: project development, provided clinical expertise and supervision, data management, and manuscript writing and editing.

Funding There is no research funding of this work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This retrospective study was approved by the Ethic Committee (EC) from the Beijing Tiantan Hospital.

Informed consent Informed consent was obtained from all individual participants included in the study.

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