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A novel intrauterine estrogen-releasing system for preventing the postoperative recurrence of intrauterine adhesion: a multicenter randomized controlled study

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Abstract

Background Transcervical resection of adhesions (TCRA) is the standard treatment for intrauterine adhesion (IUA). Previous studies have shown that postoperative oral estrogen or an intrauterine physical barrier could reduce the recurrence of IUA by promoting the proliferation of the endometrium or inhibiting the reformation of adhesions. Our team designed an intrauterine stent that can release estrogen within the uterine cavity slowly. In this study, we aimed to investigate the efficacy and safety of the estrogen-releasing intrauterine system in preventing the recurrence of moderate to severe IUA.

Methods This was a multicenter prospective randomized controlled 2-arm parallel trial that included patients who were diagnosed with moderate to severe IUA and who received TCRA. A total of 250 patients were randomly assigned, at a 1:1 ratio, to receive the intrauterine estrogen-releasing system or a Foley catheter balloon combined with oral estrogen therapy after surgery. The primary outcome was the rate of adhesion reduction in the two groups. The secondary outcomes included endometrial thickness at the ovulation period, menstrual improvement rates, and other reported adverse events during follow-up.

Results The average daily drug release amount for all the tested stents was 0.21 mg/day. At 60 days postoperatively, the rate of adhesion reduction was significantly greater in the experimental group than in the control group (93.33% vs. 58.56%, $p < 0.001$). The endometrium of the experimental group was thicker than that of the control group ($p < 0.001$). Consistently, the rate of improvement in menstruation was greater in the experimental group than in the control group ($p = 0.010$). No grade 3–4 adverse events were found in the two groups during the 1-year follow-up.

Conclusions In the cohort of patients with moderate to severe IUA, the intrauterine estrogen-releasing system was more effective at reducing adhesion than traditional oral estrogen combined with an intrauterine Foley catheter after TCRA. This novel intrauterine system provides a new option for the management of IUA after surgery.

Trial registration The registration number is NCT04972032. Date of registration: August 15, 2021.

Keywords Intrauterine adhesion, Estrogen, Releasing system, Recurrence, Transcervical resection of adhesions

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Background

Intrauterine adhesion (IUA) is caused by irreversible damage to the endometrial basal layer such as infections or trauma. It is defined by the partial or total adhesion of the uterine walls, leading to partial or complete occlusion of the uterine cavity which may lead to amenorrhea, oligomenorrhea, dysmenorrhea, infertility, and miscarriage [1]. Currently, hysteroscopy followed by transcervical resection of adhesions (TCRA) under hysteroscopy is the standard diagnosis and treatment for IUA. However, postoperative re-adhesion is common, and preventing the recurrence of IUA remains a great challenge.

The American Association of Gynecologic Laparoscopists (AAGL) and European Society of Gynecological Endoscopy (ESGE) guidelines recommend using cyclic estrogen-progestin therapy after TCRA to promote endometrial growth and repair [2]. Other strategies have also been used for preventing adhesion reformation after TCRA, including the placement of intrauterine devices (IUDs, e.g., Foley catheters, and heart-shaped Cook balloons), the use of biological gel materials or amniotic membranes, and stem cell therapy. However, there are some limitations of the current strategies, and do not yield satisfactory outcomes. For example, long-term high doses of oral estrogen increase the risk of breast cancer, endometrial cancer, venous thrombosis, etc. Intrauterine interventions also have imitations. The physical barrier area of the intrauterine contraceptive ring is limited, and the anterior and posterior walls of the uterus cannot be completely separated. Moreover, intrauterine contraceptive rings can lead to excessive inflammatory responses [1], causing abnormal bleeding, uterine infections, entrapment, and uterine perforation. Other commonly used intrauterine devices such as balloons can compress the endometrium, causing ischemic damage. Furthermore, prolonged placement of extension tubes in the vagina may increase the risk of bacterial infections in the uterine cavity and cause discomfort during movement, reducing quality of life. Thus, balloons are not suitable for long-term use [3]. Biological gel materials, such as sodium hyaluronate gel, are also used as antiadhesion materials after hysteroscopic surgery. The results of a meta-analysis investigated the effects of sodium hyaluronate gel on IUA prevention. They found that sodium hyaluronate gel can effectively prevent the reoccurrence of mild IUA, but cannot effectively prevent adhesion recurrence in patients with severe IUA [4]. Moreover, sodium hyaluronate gel has a relatively rapid degradation rate, limiting its effectiveness for preventing adhesions to only 48–72 h [5]. Consequently, sodium hyaluronate gel is only appropriate for early postoperative use. Amniotic membrane [6] and stem cells [7] are emerging strategies but are still in the early stages of research, and further testing is required to determine their effectiveness.

Due to the high recurrence rate of IUA, oral estrogen treatment and intrauterine treatment are often used together in clinical practice to promote the proliferation of the endometrium when the surgical sites within the uterine cavity are physically isolated. Whether there is a device that combines the advantages of hormone treatment and an intrauterine physical barrier without related adverse events caused by systemic treatment, such as the Mirena IUD, is unknown. Our team designed an intrauterine silicone rubber stent that can physically block the anterior and posterior walls of the uterus to prevent postoperative recurrence of adhesions (see Fig. 1). At the same time, a drug and delivery system are included in the silicone rubber, which continuously releases estradiol at a low dosage. This study aimed to further investigate the efficacy and safety of the estrogen-releasing intrauterine system in preventing the recurrence of moderate to severe IUAs.

Methods

Study design and participants

This is a multicenter prospective randomized controlled 2-arm parallel trial. Between September 2020 and January 2022, patients were recruited from four academic tertiary care centers: Beijing Tiantan Hospital, Capital Medical University (Beijing City, China); Renji Hospital, Shanghai Jiaotong University School of Medicine (Shanghai City, China); Suzhou Municipal Hospital (Suzhou City, Jiangsu Province, China); and Sir Run Run Shaw Hospital (SRRSH), Zhejiang University School of Medicine (Hangzhou City, Zhejiang Province, China). The study was conducted according to the principles of the Declaration of Helsinki and approved by the ethics committees of all participating centers.

Women were eligible if they were aged 18–40 years, diagnosed with moderate-to-severe IUA (American Fertility Society (AFS) score greater than or equal to 5 points) under hysteroscopy, and volunteered to receive the intrauterine estrogen-releasing system (experiment arm) or a Foley catheter balloon combined with oral estrogen therapy (control arm) after TCRA. Women were excluded if they were contraindicated for TCRA, used high-dose estrogen drugs within 1 month before surgery, or simultaneously suffered from genital tuberculosis, acute genital inflammatory disease, abnormal uterine bleeding, malignant tumors, or other systemic disease, such as chronic cardiocerebrovascular, liver, kidney, hematopoietic system, or psychiatric disorders. All enrolled participants provided written informed consent and agreed to the study protocol before the intervention.

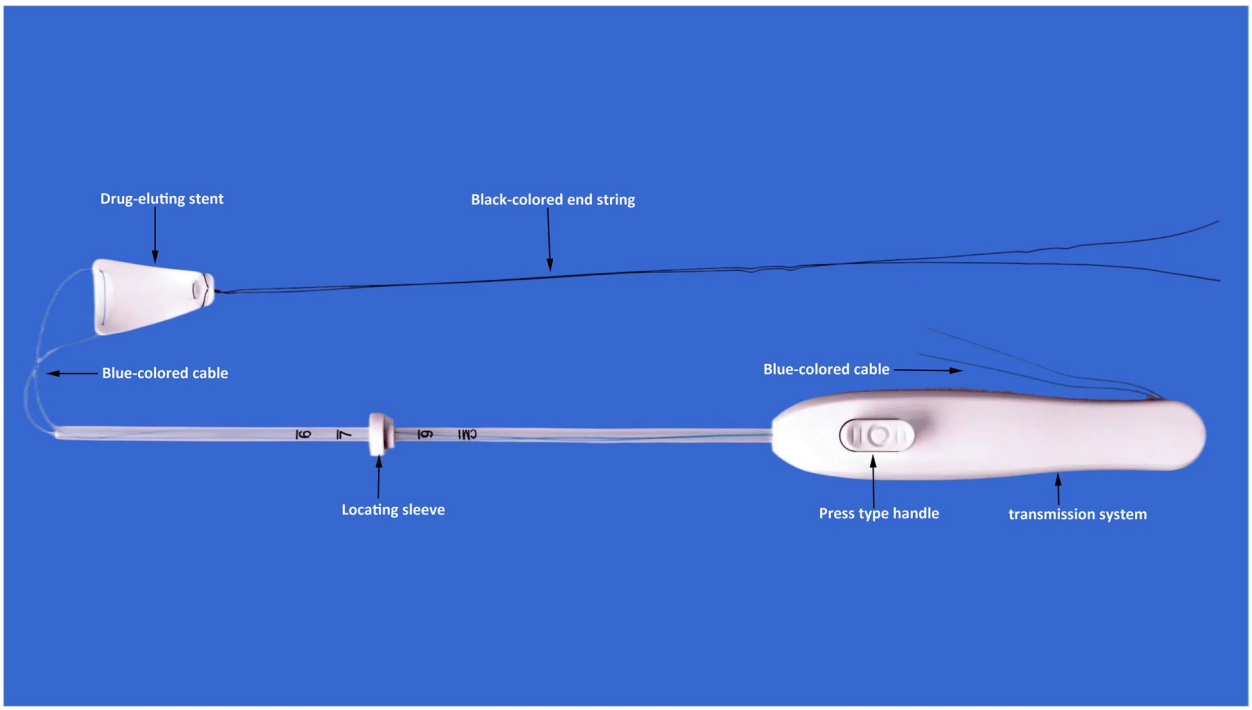

Fig. 1 Intrauterine estrogen-releasing system

Randomization and blinding

Eligible women were identified by the principal investigators in the participating centers and consented women were allocated in a 1:1 ratio to one of the two treatment arms. Enrollment at each center was performed with the use of blocks, and the participants were randomized for sample balance. SAS 9.4 software was used to generate a random assignment table. Because of the nature of the intervention, it was not possible to blind the participants or their treating doctors to the allocated treatment.

Interventions

TCRA was performed by the same surgical team at each independent center ($n=4$ teams total). After TCRA, patients in the experimental group received a silicone rubber intrauterine stent system to prevent adhesion reformation, while the control group received a Foley catheter balloon combined with self-crosslinked sodium hyaluronate gel and cyclic estrogen-progestin therapy. In the experimental group, the silicone rubber intrauterine stent system was removed 60 days after TCRA, followed by a consecutive 5-day course of dydrogesterone at 20 mg/day. Sequential estrogen-progestin therapy was administered to the control group for two cycles following the TCRA, which consisted of continuous use of estradiol valerate tablets (6 mg/day) for the first cycle, followed by the addition of dydrogesterone tablets (20 mg/day) for the second half, or continuous use of estradiol valerate tablets for 60 days (6 mg/day), followed by dydrogesterone tablets (10 mg/day) for the last 10 days (as dictated by surgical team preference).

Outcome variables

The primary outcome of this study was the rate of adhesion reduction at 60 days postoperatively. Adhesion reduction was defined as a decrease of ≥ 4 points based on AFS under hysteroscopy [8]. The severity of IUA is also evaluated by the criteria of the European Society of Gynecological Endoscopy (ESGE) classifications under hysteroscopy.

The secondary outcomes were other efficacy and safety indicators, which included endometrial thickness at the period of ovulation, menstrual improvement rates, serum estradiol levels, daily estradiol release, pregnancy rates, and other reported adverse events during follow-up.

Endometrial thickness (during the ovulation period) was evaluated through three-dimensional transvaginal ultrasound before and 60 days after surgery. Postoperative improvements in menstruation were assessed using the Pictorial Bleeding Assessment Chart (PBAC) score.

Serum estradiol levels were evaluated at 24 h, 72 h, 14 days, 30 days, and 60 days postoperatively. The remaining drug content in the intrauterine stent was evaluated 60 days after surgery. The daily release amount

was calculated as the total release amount divided by the number of days of implantation.

Pregnancy rates were assessed 1-year post-surgery. Other adverse events including uterine perforation, postoperative bleeding, pain, genital tract infection, liver or kidney injuries, and coagulation abnormalities were evaluated with CACTE 5.0 until 60 days postoperatively.

Statistical analysis

Statistical analysis was performed using SAS 9.4 statistical analysis software. All the statistical tests were two-tailed (unless otherwise specified), and a p value less than 0.05 was considered to indicate statistical significance. Mean differences were compared using paired t-test (when tests of normality and homogeneity of variance were satisfied), and categorical data were analyzed using chi-squared or Fisher's exact probability tests (when a chi-squared test was inappropriate). Ranked data were analyzed using the Cochran-Mantel–Haenszel (CMH) test.

Results

Study population and baseline information

A total of 250 patients (125 experimental patients and 125 control patients) were enrolled from the four participating sites. The baseline demographic and clinical characteristics of the two groups are shown in Table 1. There were no statistically significant between-group differences in age, height, weight, preoperative AFS score, preoperative estradiol levels, or menstrual model (evaluated by the PBAC score). Additionally, there were no differences in preoperative endometrial thickness on the day of ovulation (4.32 ± 1.73 mm vs. 4.07 ± 1.46 mm in the experimental vs. control groups).

After TCRA, the normalization rate of the uterine cavity was 100% in both groups, and all patients exhibited increased uterine volume. Both groups' AFS scores improved postoperatively, as assessed by hysteroscopy (Table 1). During the surgery, 3 patients (1 in the experimental group and 2 in the control group) who were not suitable for intrauterine device placement were evaluated. After surgery, 2 patients (1 in the experimental group and 1 in the control group) experienced the loss of the intrauterine device.

Efficacy of the intrauterine estrogen-releasing system

At 60 days post-surgery, 94.3% of the patients (231 of 245) completed the follow-up hysteroscopic evaluation, 120 of whom were in the experimental group and 111 of whom were in the control group. Fourteen patients (2 in the experimental group and 12 in the control group) did not undergo 60 days of hysteroscopy for the COVID-19 pandemic. The reduction in the number of adhesions was significantly greater in the experimental group (93.33%, 112/120) than in the control group (58.56%, 65/111) ($p < 0.001$). The degree of improvement was greater in the experimental group (−6.06 ± 2.01) than in the control group (−4.00 ± 2.45) ($p < 0.001$). The results were also validated based on the ESGE grading system: 44.17% of patients in the experimental group exhibited no adhesions (53/120), while 19.82% of patients in the control group exhibited no adhesions (22/111) ($p < 0.001$) (Table 2).

Both groups underwent ultrasound evaluation of endometrial thickness during ovulation period 60 days postoperatively. The experimental group had a significantly thicker endometrium (8.46 ± 7.37 mm) than did the control group (4.84 ± 2.48 mm) ($p < 0.001$). The rate of improvement in menstruation was also greater in the experimental group than in the control group (56.67% vs. 39.64%, $p = 0.01$).

After 12 months of follow-up, 10 patients (10.42%) in the experimental group and 12 patients (12.63%) in the control group underwent repeat TCRA ($p = 0.632$). The pregnancy rate was 31.67% (38/120) in the experimental group and 25.23% (28/111) in the control group ($p = 0.279$).

Safety of the intrauterine estrogen-releasing system

None of the patients experienced severe postoperative complications during the 1-year follow-up. The average daily drug release amount for all the tested stents was 0.21 mg/day. Serum estradiol levels were monitored at 24 h, 72 h, and 14 days postoperatively and the estradiol

Table 1 Baseline demographic and clinical characteristics ($n = 250$)

	Experimental group ($n = 125$)	Control group ($n = 125$)	p value
Age (years)	33.45 ± 4.20	33.53 ± 3.47	0.858
Height (cm)	160.08 ± 5.40	160.02 ± 4.93	0.986
Weight (kg)	56.64 ± 8.11	57.56 ± 9.27	0.511
AFS score	8.30 ± 1.71	8.23 ± 1.74	0.851
Endometrial thickness (mm)	4.32 ± 1.73	4.07 ± 1.46	0.191
Serum estradiol (pg/mL)	94.57 ± 84.99	92.60 ± 84.29	0.489

Table 2 Efficacy outcomes between two groups ($n=231$)

	Experimental group ($n=120$)	Control group ($n=111$)	*p* value
AFS score (60 days post-surgery)	2.24 ± 2.14	4.23 ± 2.86	< 0.001
Reduction in adhesions (60 days post-surgery)	112 (93.33%)	65 (58.56%)	< 0.001
Number (percentage) no adhesion (60 days post-surgery)	53 (44.17%)	22 (19.82%)	< 0.001
Number (percentage) ESGE grade I (60 days post-surgery)	27 (22.50%)	26 (23.42%)	
Number (percentage) ESGE grade II (60 days post-surgery)	26 (21.67%)	40 (36.04%)	
Number (percentage) ESGE grade III (60 days post-surgery)	9 (7.50%)	12 (10.81%)	
Number (percentage) ESGE grade IV (60 days post-surgery)	2 (1.67%)	6 (5.41%)	
Number (percentage) ESGE grade Va (60 days post-surgery)	2 (1.67%)	4 (3.60%)	
Number (percentage) ESGE grade Vb (60 days post-surgery)	1 (0.83%)	1 (0.90%)	
Endometrial thickness (60 days post-surgery) (mm)	8.58 ± 7.43	4.87 ± 2.49	< 0.001
Number (percentage) menstrual improvement (60 days post-surgery)	68 (56.67%)	44 (39.64%)	0.010
Number (percentage) total pregnancy rate	38 (31.67%)	28 (25.23%)	0.279
Number (percentage) natural pregnancy rate	21 (17.50%)	15 (13.50%)	0.404
Number (percentage) assisted reproductive pregnancy rate	17 (14.20%)	13 (11.70%)	0.579
Number (percentage) repeat TCRA	10 (10.42%)	12 (12.63%)	0.632

Table 3 Serum estradiol levels over time (pg/mL)

	Experimental group	Control group	*p* value
Baseline	94.57 ± 84.99	92.60 ± 84.29	0.489
24 h post-surgery	806.70 ± 283.88	149.35 ± 118.18	< 0.001
72 h post-surgery	697.50 ± 253.61	185.90 ± 111.26	< 0.001
14 days post-surgery	262.12 ± 240.12	214.08 ± 204.47	0.001
30 days post-surgery	143.54 ± 71.47	166.08 ± 149.99	0.948
60 days post-surgery	119.83 ± 101.28	113.13 ± 80.49	0.271

levels were significantly greater in the experimental group than in the control group ($p>0.05$). No grade 3–4 adverse events were found in the two groups during the 1-year follow-up on postoperative bleeding, pain, genital tract infections, device-related adverse events, or laboratory tests (Table 3).

Discussion

Studies have shown that postoperative oral estrogen or an intrauterine physical barrier could reduce the recurrence of IUA by promoting the proliferation of the endometrium or inhibiting the reformation of adhesions. Our team designed an intrauterine stent to release estrogen within the uterine cavity slowly. In this study, we found that this estrogen-releasing intrauterine system is more effective at reducing adhesion than traditional oral estrogen combined with an intrauterine Foley catheter after TCRA. To our knowledge, this is the first study on the use of the intrauterine estrogen-releasing system for the management of IUA after surgery.

IUA treatment usually involves surgery, preventing postoperative adhesions, promoting endometrial regeneration, and postoperative assessment of treatment efficacy, considering the etiology and risk factors associated with IUA. TCRA is the preferred surgical method for IUA. However, the high rate of adhesion reformation (up to 62.5%) after TCRA is concerning [9]. Various IUDs, including intrauterine contraceptive devices, Foley catheter balloons, and sodium hyaluronate gel, have been used to prevent postoperatively adhesion reformation. These devices serve as physical barriers and can act as carriers for certain agents that promote endometrial regeneration, such as estrogen and stem cells [10]. Estrogen can bind to estrogen receptors on the endometrium, effectively promoting the regeneration of the damaged endometrium and the formation of new blood vessels [11]. Clinical and preclinical evidence suggests that the use of estrogen in patients with IUA reduces IUA recurrence and increases pregnancy rates. In current clinical practice, a common approach for preventing adhesion reformation is the combination of a Foley catheter balloon and oral estrogen therapy. However, this method has limitations, including low drug concentrations reaching the endometrium and poor patient compliance due to the need for prolonged oral estrogen therapy. In this randomized controlled trial (RCT), a single intrauterine slow-release device was investigated as an alternative treatment that has better compliance and is more effective than traditional methods in reducing adhesions after TCRA.

Oral estrogen therapy, such as 17β-estradiol, is typically nonspecific and occurs at low concentrations in

the target tissues. To address these limitations, many methods of local administration have been explored to improve the efficacy of estrogen therapy. Local administration, such as vaginal estrogen therapy, is often an ideal approach for treating atrophic vaginitis because of its lower dosage, longer treatment time, and fewer side effects than oral medications [12]. Vaginal estrogen therapy has been commonly used for preparing the endometrium for embryo transfer. Furthermore, intrauterine stents can deliver estrogen directly into the uterine cavity, thereby targeting the endometrium. Strategies such as poly(2-hydroxyethyl methacrylate) (pHEMA) hydrogel stents [13] have been developed to release estradiol to the uterine region. The intrauterine estrogen-releasing system in our study can deliver estrogen locally at a rate of 0.21 mg/day, providing a much lower dose than oral administration (6 mg/day). Endometrial thickness undergoes cyclic changes during the menstrual cycle and thus is an important indicator of endometrial receptivity [14]. We found that the intrauterine estrogen-releasing system could be more effective at promoting endometrial proliferation than oral estrogen, which results in a thicker endometrium. Although without statistical significance, a higher tendency of pregnancy rate was observed in the experimental group than in traditional treatment group at 1-year follow-up (31.67% vs. 25.23%). The relatively low pregnancy rate of two groups may be due to the short follow-up (1 year after treatment). Long-term follow-up helps to investigate the effect of this intrauterine system on the pregnancy rates and fertility outcomes of patients.

Compared to those after oral administration of the same dosage and preparation, average serum E2 levels were approximately 10 times greater, and average endometrial E2 concentrations were approximately 70 times greater after vaginal administration [15]. A previous study suggested that estrogen receptors are highly expressed in patients with IUA [16], potentially due to decreased estrogen concentrations. However, with prolonged administration, there were no significant differences in endometrial thickness between local and systemic administration. Amir et al. [17] reported that patients with serum E2 levels between 1001 and 1500 pg/mL, 1501 and 2000 pg/mL, and > 2000 pg/mL had significantly thicker endometrial linings than patients with serum E2 levels between 0 and 1000 pg/mL. Nevertheless, endometrial thickness did not significantly differ among these three groups. This study suggested that there is a threshold effect of serum estradiol on endometrial thickness. When the serum estradiol concentration exceeds a certain threshold, its dose-dependent effect on endometrial growth ceases. This may be due to the saturation of estrogen receptors on the endometrium when exposed to high-dose estrogen. The number of estrogen receptors in the endometrium may determine its growth potential. Under the influence of high-dose estrogen, its effect may no longer depend on serum estradiol levels. Increased micro vessel density in the endometrium can promote vascular dilation and relaxation, facilitating endometrial regeneration and functional recovery [18]. However, after damage to the basal layer of the endometrium, small vessels that nourish the endometrium may also be impaired. In such cases, despite normal serum estrogen levels, estrogen cannot be effectively transported to the endometrium through damaged endometrial vessels. Previous research revealed no differences in treatment efficacy or pregnancy rates between high-dose and low-dose oral estrogen therapy [19]. High-dose estrogen can overload and damage the liver and can lead to adverse effects in target organs, including breast pain, breast cancer, cervical thrombosis, and even endometrial fibrosis [20]. The adverse effects mentioned above do not occur when serum estradiol levels are greater than 1000 pg/mL for 2 weeks [15, 21]. Peak serum estradiol levels occurred on days 1–3 and were approximately 800 pg/mL after the use of the new estrogen sustained-release stent, which further supports its safety. Short-term high-dose estrogen therapy may promote endometrial proliferation. However, after postoperative day 14, the serum estrogen levels of the experimental group decreased and were similar to those of the control group. Compared to those in the control group, no intrauterine estrogen stent-related adverse events were found at the 1-year follow-up in this study.

Conclusions

In conclusion, our study reports an intrauterine estrogen-releasing system for the management of IUA after TCRA that combines the advantages of estrogen treatment and an intrauterine stent. The results showed that the intrauterine estrogen-releasing system is more effective at reducing adhesion than traditional oral estrogen combined with an intrauterine Foley catheter after TCRA. This novel intrauterine system is tolerable and provides a new option for the management of this population.

Abbreviations

TCRA	Transcervical resection of adhesions
IUA	Intrauterine adhesion
AAGL	The American Association of Gynecologic Laparoscopists
ESGE	European Society of Gynecological Endoscopy
AFS	American Fertility Society
PBAC	Pictorial Bleeding Assessment Chart
CMH	Cochran-Mantel-Haenszel
RCT	Randomized controlled trial

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Authors' contributions
LF, YS, SZ1, and YQ conceived and designed the study. LF and YS supervised the study and data analysis. LF, YS, SZ1, and YQ performed the operation as the lead surgeons. SF, BY, LX, JL, YN, SZ2, LZ and JC assisted in analyzing the data and the operation. LF and YS wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon request.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Beijing Tiantan Hospital, Capital Medical University, on October 22, 2019. The Ethics Committee approval number is QX2019-008-02. All participants enrolled in the present trial provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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