



Review Article

Meta-analysis on the use of hyaluronic acid gel to prevent recurrence of intrauterine adhesion after hysteroscopic adhesiolysis

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ABSTRACT

Intrauterine adhesion is a severe complication after intrauterine operation. Various adjuvant therapies failed to improve clinical symptoms and pregnancy rates among patients with moderate-to-severe intrauterine adhesion. At present, hyaluronic acid gel is widely used in the primary prevention of adhesion after hysteroscopic adhesiolysis. However, its efficacy is still under debate. Therefore, the aim of this study was to systematically evaluate the efficacy of hyaluronic acid gel in preventing the recurrence of intrauterine adhesion after hysteroscopic adhesiolysis. The Cochrane Library, Embase, and PubMed databases were used to search for articles published before July 31, 2018, using the following terms: hyaluronic acid, intrauterine adhesions, Asherman's syndrome, IUA, hysteroscopy, and hysteroscopic adhesiolysis. Studies on therapies after hysteroscopic adhesiolysis were collected. The recurrence rate of and pregnancy rate in the presence of intrauterine adhesion after hysteroscopic adhesiolysis were analyzed by RevMan 5.3 software. A total of 6 articles were selected, which included 394 patients who were subjected to hysteroscopic adhesiolysis. The meta-analysis results showed that (1) no statistically significant difference was found between hyaluronic acid gel use and without its use on the score of intrauterine adhesion after hysteroscopic adhesiolysis [the mean difference (MD) = −0.89, 95% confidence interval (CI) (−2.53–0.76), $P = 0.29$], neither a statistically significant difference was observed between the same groups on the recurrence rate of intrauterine adhesion [odds ratio (OR) = 0.75, 95% CI (0.31–1.81), $P = 0.53$]; (2) subgroup analysis showed that hyaluronic acid gel could reduce the rate of intrauterine adhesion recurrence in randomized controlled trials [OR = −0.28, 95% CI (0.14–0.56), $P = 0.0006$]. However, the recurrence rate of intrauterine adhesion after the use of hyaluronic acid gel was not statistically significant in non-randomized controlled experiments [OR = 1.53, 95% CI (0.79–2.95), $P = 0.21$]; (3) hyaluronic acid gel did not result in a significant effect on pregnancy rate after intrauterine adhesion separation [OR = 2.02, 95% CI (0.53–7.66), $P = 0.3$]. In conclusion, hyaluronic acid gel could reduce the recurrence rate of intrauterine adhesion, but had no significant effect on the postoperative pregnancy rate.

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Introduction

Intrauterine adhesions, also known as Asherman's syndrome, are a consequence of lesions of the endometrial basement caused by various factors, such as intrauterine operation and infection. In the process of repair, the endometrium forms adhesions and scars

in the uterine cavity, resulting in an abnormal uterine morphology [1,2]. There are several main clinical manifestations of intrauterine adhesion, including menstrual reduction, recurrent abortion, amenorrhea, recurrent lower abdominal pain, and infertility, which seriously endanger women's health [3,4]. At present, the most effective method to treat intrauterine adhesion is hysteroscopic adhesiolysis, however the rate of re-adhesion formation after surgery is still high. In a previous study, it was reported that the re-adhesion rate after severe intrauterine adhesion surgery is up to 62.5% [5]. Therefore, it is of utmost importance to prevent this recurrence after hysteroscopic adhesiolysis [6–9]. In previous

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studies, it was shown that hormones, intrauterine balloon, intrauterine device (IUD), and amniotic membrane achieved a certain curative effect in preventing intrauterine adhesion, however no clear effect was observed in improving the clinical symptoms and pregnancy rate [6–9]. At present, hyaluronic acid gel is widely used in the primary prevention of adhesions after intrauterine operation [10,11]. Hyaluronic acid gel has achieved several good effects, however its efficacy in preventing adhesion recurrence and improving the pregnancy rate is still unclear. Therefore, the aim of the present study was to conduct a meta-analysis of all published trials on the use of hyaluronic acid gel to evaluate its effects in preventing the recurrence of intrauterine adhesion after hysteroscopic adhesiolysis (see Table 1).

Materials and methods

Retrieval strategy

For the database search, the following terms were used: hyaluronic acid, intrauterine adhesions, Asherman's syndrome, IUA, hysteroscopy, and hysteroscopic adhesiolysis. The following databases were used: PubMed, EMBASE, and the Cochrane Library, and the search was performed on studies published before July 31, 2018, without language restrictions.

Literature screening

The screening included the following steps: (1) Research type: study on the use of hyaluronic acid gel after hysteroscopic adhesiolysis, (2) Subjects inclusion criteria: women at childbearing age who underwent hysteroscopic adhesiolysis. More than two groups of trials were considered (use or no use of hyaluronic acid gel as an adjunctive therapy after hysteroscopic adhesiolysis).

Exclusion criteria: case reports; studies that do not provide specific results; an studies with an unreasonable design of experiments.

Quality evaluation and data statistics

Literature screening, bias risk assessment, and data extraction were independently conducted by two evaluators. Risk assessment methods were performed using the evaluation method recommended by the Cochrane reviewers' handbook 5.1 [12]. Data were analyzed using the RevMan 5.3 software provided by the Cochrane collaboration. The statistical heterogeneity of each study was analyzed by χ^2 , and the significant level was set at $P = 0.1$. $P < 0.1$

indicated statistical heterogeneity of the study. I^2 was used to quantitatively evaluate the heterogeneity of the results. An I^2 less than 25% suggested that heterogeneity may not be important; I^2 greater than 50% indicated significant heterogeneity; and I^2 greater than 75% indicated a high degree of heterogeneity. Analysis for a combined effect size was not performed. When I^2 was greater than 50%, the random effect model was adopted, and subgroup analysis and sensitivity analysis were performed. When I^2 was less than 50%, a fixed effect model was adopted. All participants were included in the analysis, and included trials were divided into a treatment group treated with hyaluronic acid gel and control group according to the type of intervention, such as whether hyaluronic acid gel was used for adjuvant therapy after hysteroscopic adhesiolysis or not. The outcome was measured with a dichotomous variable represented by the odds ratio (OR) and 95% confidence interval (CI), and the continuous variables were represented by the mean difference (MD).

Evaluation index

In this study, main outcome indicators were as follows: (1) Incidence of intrauterine adhesions: the number of intrauterine adhesions cases/total cases, evaluated by the grading method of the American fertility society (AFS) in 1988 [13]; (2) Pregnancy rate: number of pregnancies/total cases.

Results

Basic features included in the study

A total of 282 studies were initially examined, and 6 studies were included in the final screening (all studies involved the comparison of efficacy of adjuvant therapy with hyaluronic acid gel after hysteroscopic adhesiolysis and adjuvant therapy without hyaluronic acid gel, Fig. 1. A total of 394 women at childbearing age after intrauterine adhesion separation was considered, and among them, 176 women were treated with hyaluronic acid gel after surgery. In addition, a total of 218 women were not treated with hyaluronic acid gel after surgery. One study considered a woman treated with intrauterine balloon therapy [19] and one study considered a woman treated with an oral antibiotic [15]. Fig. 1 shows that no statistically significant differences were observed in baseline data between the treatment group and the control group [14–19]. Results of study quality assessment are shown in Fig. 2, among which two studies included randomized controlled studies [15,19] in which the specific allocation concealment method

Table 1
General information of the included literature.

Study (first author)	study type	N	disease	Intervention	Outcomes
Ducarme 2006 [14]	prospective cohort study	18	intrauterine adhesions	Gel and Hysteroscopic adhesiolysis vs Hysteroscopic adhesiolysis	IUAs recurrence
Giuseppe 2003 [15]	RCT	84	intrauterine adhesions	Gel, oral antibiotics and Hysteroscopic adhesiolysis vs oral antibiotics and Hysteroscopic adhesiolysis	IUAs recurrence, IUAs score
Krajčovičová 2015 [16]	prospective cohort study	32	mild, moderate to severe IUAs	Gel and Hysteroscopic adhesiolysis vs Hysteroscopic adhesiolysis	pregnancy
Lin 2013 [17]	retrospective cohort study	59	mild, moderate to severe IUAs	Gel and Hysteroscopic adhesiolysis vs Hysteroscopic adhesiolysis	IUAs recurrence
Thubert 2015 [18]	retrospective cohort study	90	mild, moderate to severe IUAs	Gel and Hysteroscopic adhesiolysis vs Hysteroscopic adhesiolysis	IUAs recurrence, IUAs score, pregnancy
Xiao 2015 [19]	RCT	111	moderate to severe IUAs	Gel, Foley's catheter balloon and Hysteroscopic adhesiolysis vs Foley's catheter balloon and Hysteroscopic adhesiolysis	IUAs recurrence, IUAs score

Abbreviations: IUAs, intrauterine adhesions; RCT, randomized controlled trial.

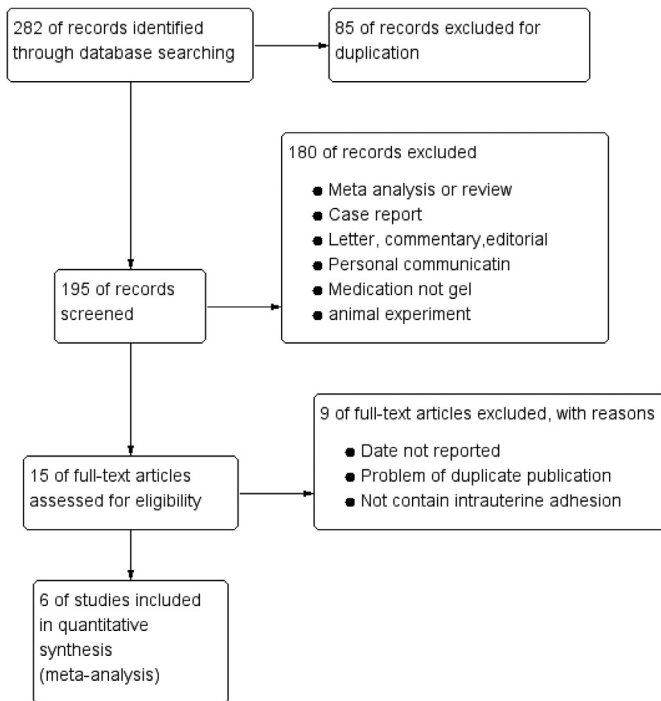


Fig. 1. Flowchart depicting the method of study selection.

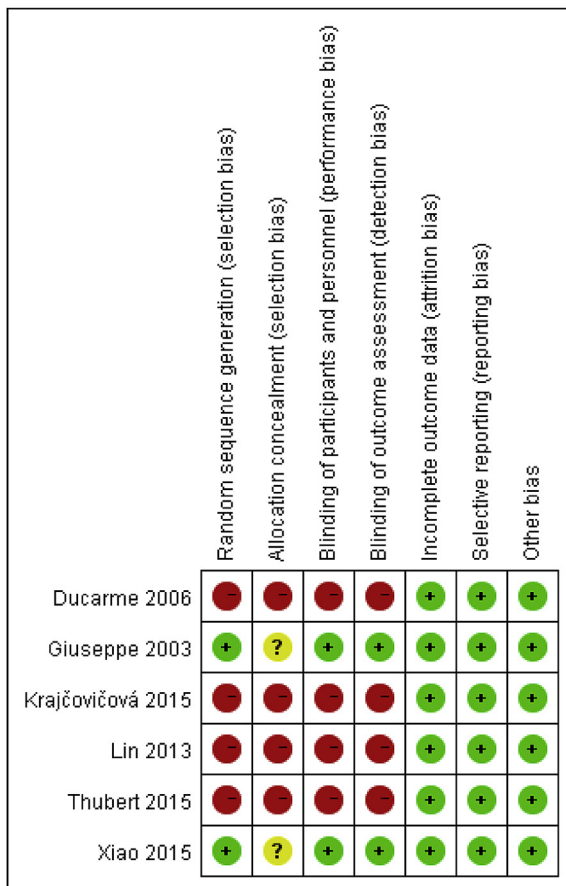


Fig. 2. Biased risk assessment chart of studies included in the meta-analysis ($n = 4$). Green indicates a low risk of bias, yellow indicates unclear risk of bias, and red indicates a high risk of bias.

was not explained. Four studies included non-randomized controlled studies [14,16–18].

Meta-analysis results

In three studies, the score of intrauterine adhesion after hysteroscopic adhesiolysis was reported [15,18,19], and in six studies the recurrence rate of intrauterine adhesion after hysteroscopic adhesiolysis was reported [14,15,17–19]. The results of the meta-analysis showed that hyaluronic acid gel had no significant effect on the postoperative intrauterine adhesion score after hysteroscopic adhesiolysis [OR = -0.89 , 95% CI (-2.53 – 0.76), $P = 0.29$]. Figs. 3 and 4 show that the recurrence rate of intrauterine adhesion was not statistically significant [OR = 0.75 , 95% CI (0.31 – 1.81), $P = 0.53$]. Since the included literature had high heterogeneity, subgroup analysis demonstrated that hyaluronic acid gel reduced the recurrence rate of intrauterine adhesion in the randomized controlled trial [OR = -0.28 , 95% CI (0.140 – 0.56), $P = 0.0006$] (Fig. 5). In the non-randomized controlled trial, hyaluronic acid gel did not significantly reduce the recurrence rate of intrauterine adhesion [OR = 1.53 , 95% CI (0.79 – 2.95), $P = 0.21$, Fig. 5]. Furthermore, sensitivity analysis was employed, and no studies that significantly resulted in changes in heterogeneity were identified. In two studies [16,18], the effect of hyaluronic acid gel on the pregnancy rate was reported, and the data showed that the pregnancy rate after intrauterine adhesion separation with or without the use of hyaluronic acid gel was not statistically significant [RR = 2.02 , 95% CI (0.53 – 7.66), $P = 0.3$, Fig. 6]. Thus, the results indicated that hyaluronic acid gel may reduce the recurrence rate of intrauterine adhesion, but had no significant effect on the postoperative pregnancy rate.

Discussion

Intrauterine adhesions mainly occur in young women, thereby seriously endangering female reproductive system. Available treatment methods for intrauterine adhesions are limited. Hysteroscopic adhesiolysis and adjuvant therapies, including hormones, intrauterine devices, and intrauterine balloons have been moderately successful in treating intrauterine adhesions [6–9]. However, no clear improvement in clinical symptoms and pregnancy rates has been observed among patients with moderate-to-severe intrauterine adhesions who underwent such adjuvant therapies [6–9]. Hyaluronic acid gel has been widely used to prevent postoperative adhesions and endometrial regeneration after hysteroscopic adhesiolysis [10,11]. The aim of the present study was to conduct a meta-analysis of all published trials on the systematic use of hyaluronic acid gel to prevent the recurrence of intrauterine adhesions after hysteroscopic adhesiolysis.

Three studies [15,18,19] included in this work reported the score of intrauterine adhesions after hysteroscopic adhesiolysis. Moreover, the recurrence rate of intrauterine adhesions after intrauterine adhesion separation was reported in 6 studies [14,15,17–19]. The results of the current study indicated that hyaluronic acid gel did not show improvement in the score of intrauterine adhesions after hysteroscopic adhesiolysis. Thus, hyaluronic acid gel could not reduce the recurrence rate of intrauterine adhesions. In two studies [16,18], the effect of this treatment on the pregnancy rate was reported, and the results showed no improvement in the pregnancy rate after hysteroscopic adhesiolysis by hyaluronic acid gel. However, neither of the two studies [16,18] reported in detail the use of contraceptives after treatment, nor the sufficient follow-up time, thus, it was impossible to truly assess the effect of hyaluronic acid gel on the postoperative pregnancy rate. In addition, the results of this study indicated that two studies [15,19] involved randomized

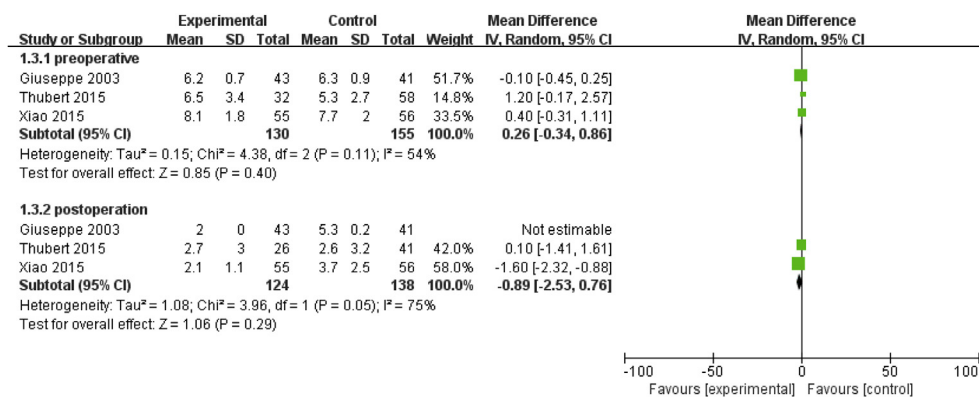


Fig. 3. Forest plot of intrauterine adhesion score after hysteroscopic adhesiolysis. Abbreviations: CI, confidence interval; df, degrees of freedom; IV, inverse variance.

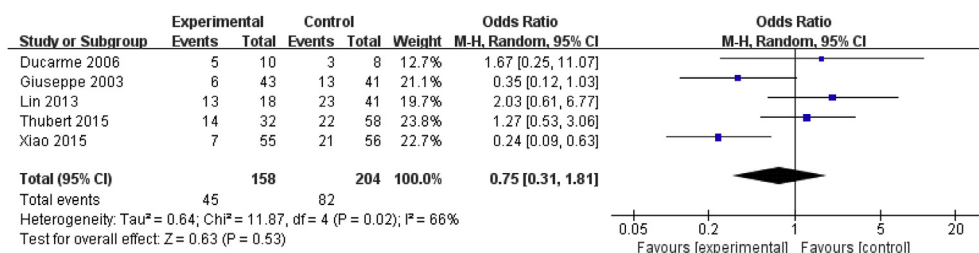


Fig. 4. Forest plot of the incidence of intrauterine adhesions after hysteroscopic adhesiolysis. Abbreviations: CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel.

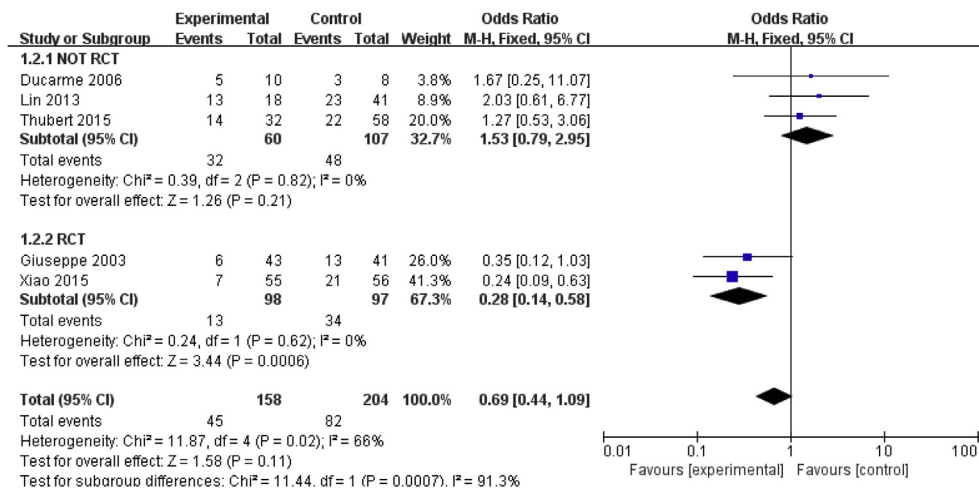


Fig. 5. Forest plot of the recurrence rate of intrauterine adhesion after hysteroscopic adhesiolysis in non-randomized controlled trials and randomized controlled trials. Abbreviations: CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel.

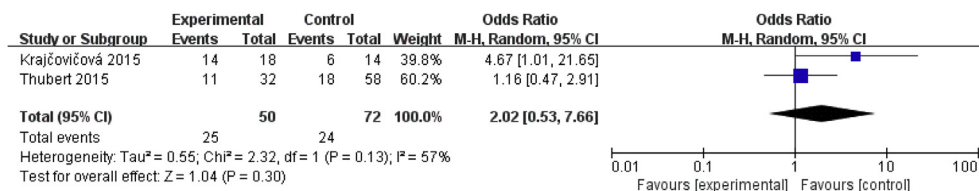


Fig. 6. Forest plot of pregnancy rate after hysteroscopic adhesiolysis. Abbreviations: CI, confidence interval; df, degrees of freedom; M-H, Mantel–Haenszel.

controlled trials, in which hyaluronic acid gel could reduce the rate of intrauterine adhesion recurrence. Furthermore, four articles [14,16–18] included non-randomized controlled trials, in which

hyaluronic acid gel did not reduce the rate of intrauterine adhesion recurrence. The results of the current study were mainly influenced by the type of study in the articles considered. Therefore, the

efficacy of hyaluronic acid gel in preventing intrauterine adhesion recurrence and in improving the pregnancy rate should be determined by randomized controlled trials with a large sample size.

Hyaluronic acid is a polymer mucopolysaccharide that was initially isolated and purified by Meyer et al. [20] from the bovine vitreous in 1934, and represents an important component of the extracellular matrix. Hyaluronic acid has an effect on migration, proliferation, and differentiation of cells, and can interact with cytokines to retain itself in the microenvironment of extracellular matrix [21]. Hyaluronic acid can bind many water molecules and thereby improves tissue hydration, enhances cell resistance to mechanical injury, and reduces post-traumatic granulation tissue and fibrous tissue formation [22,23]. Due to its unique biocompatibility and enzymatic biodegradation, hyaluronic acid is often used to prevent postoperative tissue adhesion [22,23]. In addition to physical effects, such as covering and blocking wound surface, hyaluronic acid gel also inhibits postoperative bleeding and inflammatory bleeding, avoids fibrinosis on the tissue contact surface, effectively inhibits the migration and phagocytosis of granulocytes, reduces platelet deposition, and has several anti-inflammatory effects [24,25]. Because natural hyaluronic acid is easily degraded *in vivo*, its biological efficacy is limited. By combining hyaluronic acid gel with other biological polymers, hyaluronic acid gel is transformed into biological products related to hyaluronic acid through esterification and cross-linking of hyaluronic acid itself, such as hyaluronic acid-carboxymethyl cellulose gel, which is widely used to prevent tissue adhesion after surgery [21]. In recent years, the preventive effect of hyaluronic acid gel on intrauterine adhesion has attracted much attention. Huberlant SStephanie H. et al. [26] demonstrated that the use of hyaluronic acid gel in animal models improved fertility and reduced the incidence of intrauterine adhesion. Vassilios et al. [27] divided 150 patients into two groups, the experimental group was treated with Septrafilm after Dilatation and Curettage (D&C), whereas the control group was not treated with Septrafilm after D&C. The data showed that Septrafilm treatment in 32 patients resulted in a pregnancy rate of 100%, whereas in the control group, the pregnancy rate was only 54% [27]. Krajčovičová et al. [16] showed that after hysteroscopic adhesiolysis, the probability of restoring a normal menstrual cycle using hyaluronic acid gel was 60.0%, the probability of restoring a normal menstrual cycle with postoperative implantation of an IUD was 55.5%, and the probability of restoring a normal menstrual cycle in the control group was 36.3%. The pregnancy rate of patients treated with hyaluronic acid gel was 77.7%, which was significantly higher than that in patients treated with an IUD (60%). Therefore, the application of hyaluronic acid gel after intrauterine adhesion separation can significantly improve the pregnancy rate.

In summary, hyaluronic acid gel may reduce the recurrence rate of intrauterine adhesion, but has no significant effect on increasing the postoperative pregnancy rate. However, hyaluronic acid gel is widely used in the primary prevention of adhesions after intrauterine operation [10,11] and achieved certain effects for a long period of time. Thus, our data could be mainly due to the limitation of the study design and small sample size of the included studies. In our meta-analysis, 6 studies showed significant overall heterogeneity, which was mainly derived from the different types of research performed. Four articles included in this study were non-randomized controlled trials with small sample size and short follow-up time, which may have influenced our analysis results. Therefore, a larger sample size, longer follow-up, and more well-designed, randomized, controlled clinical studies are required to investigate the efficacy of hyaluronic acid gel in the prevention of intrauterine adhesion after hysteroscopic adhesiolysis. The results of this study suggested that hyaluronic acid gel can be used in

randomized controlled trials to prevent intrauterine adhesion after hysteroscopic adhesiolysis, thereby preventing intrauterine adhesion.

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Authors'contributions

Zheng Fei and Zhu Bin contributed equally to this work.

Conflicts of interest statement

The authors have no conflicts of interest relevant to this article.

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