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Systematic Review

Efficacy of Reducing Recurrence of Intrauterine Adhesions and Improving Pregnancy Outcome after Hysteroscopic Adhesiolysis: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: A systematic review with pairwise and network meta-analyses was conducted to compare the clinical efficacy of treatments in reducing intrauterine adhesion (IUA) recurrence and improving pregnancy outcome after hysteroscopic adhesiolysis. **Methods**: PubMed, Web of Science, Embase, Cochrane library, and Clinicaltrials.gov were searched electronically up to January 17th, 2024, supplemented with manual searches. Eligible studies were randomized clinical trials (RCTs) with allocation to intrauterine device (IUD), auto-cross-linked hyaluronic acid (ACP), medical chitosan (MC) + IUD, Foley (Foley balloon catheter 3–7 days) + IUD, heart shape balloon (HSB), dried amnion graft or bone marrow stem cells-scaffold or granulocyte colony-stimulating factor (DBG) + Foley/HSB, autologous platelet gel or platelet-rich plasma (APG/PRP) + IUD/HSB, ACP + Foley/IUD, Foley, and heart shape balloon or Foley 1 month (H/F) + IUD. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Pairwise meta-analyses were performed in random effects model when direct data were available; Network meta-analyses were conducted using "mvmeta" and "network" packages in Stata MP 17.0. The primary outcomes were the recurrence of IUA and clinical pregnancy. The secondary outcomes included menstrual blood volume and second-look IUA score. The research protocol was registered in PROSPERO (CRD42024502941). **Results**: Fifteen RCTs comprising 1827 patients randomized to ten treatment protocols were included in this study. Evidence quality was all low risk of bias. ACP and Foley + IUD (surface under the cumulative ranking curve area (SUCRA) 96.4% and 83.5%, respectively) seemed effective in reducing the recurrence of IUA, H/F + IUD and DBG + Foley/HSB (SUCRA 89.7% and 82.1%, respectively) maybe effective in improving the clinical pregnancy according to network meta-analysis. Evidence on secondary treatment outcomes was insufficient. **Conclusions**: Some of these protocols maybe effective in reducing the recurrence of IUA or increasing clinical pregnancy. But the result should be interpreted with caution owing to the small studies, open-loop network analysis partly, and insufficient evidence. More RCTs about DBG + Foley/HSB needs to be designed, the relative effectiveness of different degrees of IUA treatment should be further clarified, and more attention should be paid to clinical pregnancy, menstrual flow, and second-look IUA score.

Keywords: intrauterine adhesions; hysteroscopic adhesiolysis; recurrence of intrauterine adhesions; pregnancy outcome; network meta-analysis

1. Introduction

Intrauterine adhesion (IUA) is an abnormal healing after the basal layer of endometrium is damaged by trauma, infection, or other reasons. IUA is usually characterized by endometrial fibrosis and scarring, endometrial thinning and loss, hyperplasia, hyposecretion, adhesion of the front and rear walls of the uterus to varying degrees, and uterine cavity volume reduction or even complete occlusion. Adhesions of different natures and positions can cause amenorrhea, oligomenorrhea, periodic lower abdominal pain, infertility, habitual abortion, and other symptoms [1]. The incidence of IUA varies with different populations and diagnostic criteria. Israel has the highest incidence (22.8%) globally, followed by Greece (15.3%) and South America (14.9%) [2]. Currently, the main treatment method for IUA is hysteroscopic adhesiolysis. However, the recurrence rate

of IUA is as high as 1 in 3 women with mild to moderate IUA [3], and up to 62.5% for severe IUA [2]. Furthermore, the rate of pregnancy is only 45.9% [4]. Therefore, prevention of IUA recurrence and promotion of pregnancy following hysteroscopic adhesiolysis is the key to successful treatment.

Several types of physical barrier have been proposed to reduce the formation of IUAs after hysteroscopic adhesiolysis, including postoperative hormone treatment, intrauterine device placement, Foley balloon catheter, auto-cross-linked hyaluronic acid, and chitosan [5–9]. In recent years, new bioactive factors or biomaterials have been employed for their potential to repair the endometrium, such as dry amnion-Foley balloon, granulocyte colony-stimulating factor (G-CSF), autologous bone marrow stem cells-collagen scaffold, and autologous platelet gel [5,10–13]. In addition, all methods may be used in various combinations or for different durations. However, despite the proposal of many methods, there is no consensus on the best measure to prevent the formation of IUA and improve the pregnancy rate.

Hormone treatment may reduce the recurrence of IUA according to the American Association of Gynecologic Laparoscopists (AAGL) [3]; consequently, most existing studies have used hormone therapy in combination with other postoperative treatment options. To compare the clinical efficacy of various treatments in reducing IUA recurrence and improving pregnancy outcome and to guide future clinical treatment, we conducted a systematic review and meta-analysis of data from published randomized controlled trials (RCTs) that used any postoperative preventive measures for IUA after hysteroscopy based on hormone treatment.

2. Materials and Methods

2.1 Search Strategy and Selection Criteria

For this systematic review and network meta-analysis, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. We searched PubMed, Web of Science, Embase, and Cochrane library databases using the keywords and Medical Subject Heading (MeSH) terms “IUA” and “randomized controlled trial” (**Supplementary file 1**) from database inception to January 17th, 2024, supplemented with manual searches. We also searched Clinicaltrials.gov to secure additional RCTs. The research protocol was registered in PROSPERO (registration code CRD42024502941).

The inclusion criteria were: (1) participants had IUA diagnosis according to hysteroscopy findings; (2) participants had a mean age 25 to 35 years; (3) participants underwent hysteroscopic adhesiolysis followed by the application of at least one antiadhesion or endometrium repair treatment; (4) participants carried out a second-look hysteroscopy to diagnoses whether IUA recurrence or not; (5) use pictorial blood-loss assessment chart (PBAC) score to evaluate menstrual blood score [15]; (6) RCT study. The exclusion criteria were: (1) study that compared the same adjuvant treatment; (2) study with repeated use of the same treatment; (3) animal study.

2.2 Outcome Measures

The primary outcomes were the recurrence of IUA and clinical pregnancy. A second-look hysteroscopy was performed to make clear the recurrence of IUA. Clinical pregnancy was defined as the presence of a gestational sac with or without a fetal heartbeat by ultrasound. Secondary outcomes included menstrual blood score and second-look IUA score in case of adhesion recurrence. Menstrual blood score was assessed by PBAC before the second-look hysteroscopy, second-look IUA score was evaluated according to the classification method of the American Fertility Society (AFS) [16].

2.3 Risk of Bias Assessment

The risk of bias for each included trial was evaluated by The Cochrane tool [17]. Potential sources of bias include the aspects of random sequence generation, allocation concealment, blinding of participants and staff, blinding of outcome assessors, incomplete outcome data, selective reporting, and other bias. Each trial received a study level score of low, high, or unclear risk of bias for each aspect. The risk of bias assessment was judged by two authors (LJL and XYQ) independently, and disagreement were resolved by discussion.

2.4 Data Extraction

Two independent investigators extracted data from the original reports. Specially designed forms were used to collect information on study design, country, patients’ characteristics, sample size, details of adjuvant treatments, hysteroscopic adhesiolysis procedure, menstrual blood volume, second-look IUA score, and pregnancy outcome. Continuous variables represented by medians and quartiles (or interval) were converted to means and standard deviations according to the methods described in Luo D literature [18]. Data that could not be extracted from the original publication were requested from the corresponding author.

2.5 Data Synthesis and Statistical Analysis

Paired meta-analyses were conducted in the random effect model when direct data were available. Heart shape balloon (HSB) placed in uterus for days based on hormone therapy was regarded as the control group. The “mvmeta” and “Network” packages in Stata MP 17.0 (developed by StataCorp, headquartered in College Station, TX, USA) were used for network meta-analyses. For each interested result, the command < network element inconsistency > was used to statistically confirm the global consistency hypothesis between networks by fitting the design-by-treatment interaction model, which provided a global

Wald test to evaluate the inconsistency in the whole network [19,20]. The Separating Indirect from Direct Evidence (SIDE)-splitting method using the command < network sidesplit all > was used for the local test when closed loop existed [21]. When $p > 0.05$ indicated that there was no significant inconsistency between the direct comparison and the indirect comparison, and pairwise comparisons were made between different interventions. Network geometry and node connectivity were visualized for all outcomes. For all treatment comparisons, we gave the comprehensive odds ratio (OR) or mean difference and 95% confidence interval (95% CI), which explained the uncertainty of variance estimation in the ranking. We also provided the comprehensive processing effect of 95% confidence intervals of all comparisons in forest plots. To obtain the treatment grade, the effectiveness of each intervention was ranked by the surface under the cumulative ranking curve area (SUCRA), the higher the ranking, the greater the possibility of becoming the best intervention.

2.6 Small Study Effects

To evaluate the presence of small study effects, we visually inspected comparison adjusted funnel plots for each outcome. Funnel plots for all comparisons are also presented.

3. Results

3.1 Search Results and Baseline Characteristics

A total of 1815 studies were identified through the database search. Among them, 1024 studies were duplicated and were deleted. After screening the titles and abstracts, 751 studies were deleted. Of the remaining 40 studies that were evaluated in full text, 10 were not RCTs so were removed, 11 were deleted because the intervention group and the control group compared the same adjuvant treatments, and 4 trials were excluded because they repeated used the same adjuvant treatment which were different from other included trials obviously. Consequently, 15 studies were included for network meta-analysis [5–13,22–27]. The literature search process is described in a flowchart (Fig. 1). **Supplementary file 2** provides the full citations of the included trials, and **Supplementary file 3** provides details of the excluded trials after evaluating the full text. **Supplementary Fig. 1A,B** presents the results for the assessment of risk of bias. Briefly, all of the included trials were considered low risk of bias, with none classified as moderate or high risk. The included studies comprised 1827 participants diagnosed with IUA and who received one of the ten different antiadhesion based on the hormone treatment, including intrauterine device (IUD), auto-cross-linked hyaluronic acid (ACP), medical chitosan (MC) + IUD, Foley (Foley balloon catheter 3–7 day) + IUD, heart shape balloon (HSB), dried amnion graft or bone marrow stem cells-scaffold or G-CSF (DBG) + Foley/HSB, autologous platelet gel or platelet-rich plasma (APG/PRP) + IUD/HSB, ACP + Foley/IUD, Foley, heart shape balloon or Foley 1 month (H/F) + IUD.

The mean age of participants ranged from 25 to 33 years in the 15 studies included in this research. The basic characteristics of the studies included in the network meta-analysis are summarized in **Supplementary Table 1**. Hysteroscopic adhesiolysis was performed with a 4.5–5-mm office hysteroscope in five studies [5,10,12,23,25], whereas an 8.5-mm rigid hysteroscope was used in four studies [7–9,11], and one study employed a 5-mm office hysteroscope initially, but switched to an 8.5-mm rigid hysteroscope when met with thick fibrosis [22]. The remaining five trials did not state the type of hysteroscope used [6,13,24,26,27]. Microscissors without energy were used for adhesiolysis in five studies [12,13,23,25,26], monopolar energy was used in two studies [5,6], five trials opted for bipolar energy resection [7–11], one study utilized a plasma electric cutting needle for adhesiolysis [27], one study employed 5F pointed tips or semirigid scissors (except in patients with thick fibrous adhesions, where lysis was performed with a hysteroscopic monopolar knife) [22], and one study did not state the type of hysteroscopic surgical instruments used [24]. Postoperative hormonal treatment was administered in all the included studies. The follow-up period varied from 1 to 60 months.

3.2 Pairwise Meta-Analysis

Supplementary Fig. 2A,B presents the pairwise meta-analysis results for IUA recurrence and clinical pregnancy, respectively. Briefly, dried amnion graft or bone marrow stem cells scaffold or granulocyte colony-stimulating factor (DBG) + Foley/HSB showed no advantages in reducing the recurrence of IUA compared with the control (odds ratio (OR) = 0.84, 95% confidence interval (95% CI) 0.57, 1.24). For clinical pregnancy, DBG + Foley/HSB was advantageous compared with the control (OR = 2.11, 95% CI 1.34, 3.33)

3.3 Network Meta-Analysis

The network plots of primary outcomes are presented in **Supplementary Fig. 3A,B**. For primary outcomes of IUA recurrence and clinical pregnancy, 13 and 8 studies, respectively, were available for analysis across all treatments. As shown in **Supplementary Fig. 3A,B**, the comparisons of recurrence of IUA in Foley + IUD, dried amnion graft or bone marrow stem cells-scaffold or granulocyte colony-stimulating factor (DBG) + Foley/HSB, medical chitosan (MC) + IUD, and heart shape balloon or Foley 1 month (H/F) + IUD were compared in open loops, and the comparisons of clinical pregnancy in DBG + Foley/HSB and autologous platelet gel or platelet-rich plasma (APG/PRP) + IUD/HSB were compared in open loops.

The netleague analyses of the reduction of IUA recurrence are presented in Fig. 2. Auto-cross-linked hyaluronic

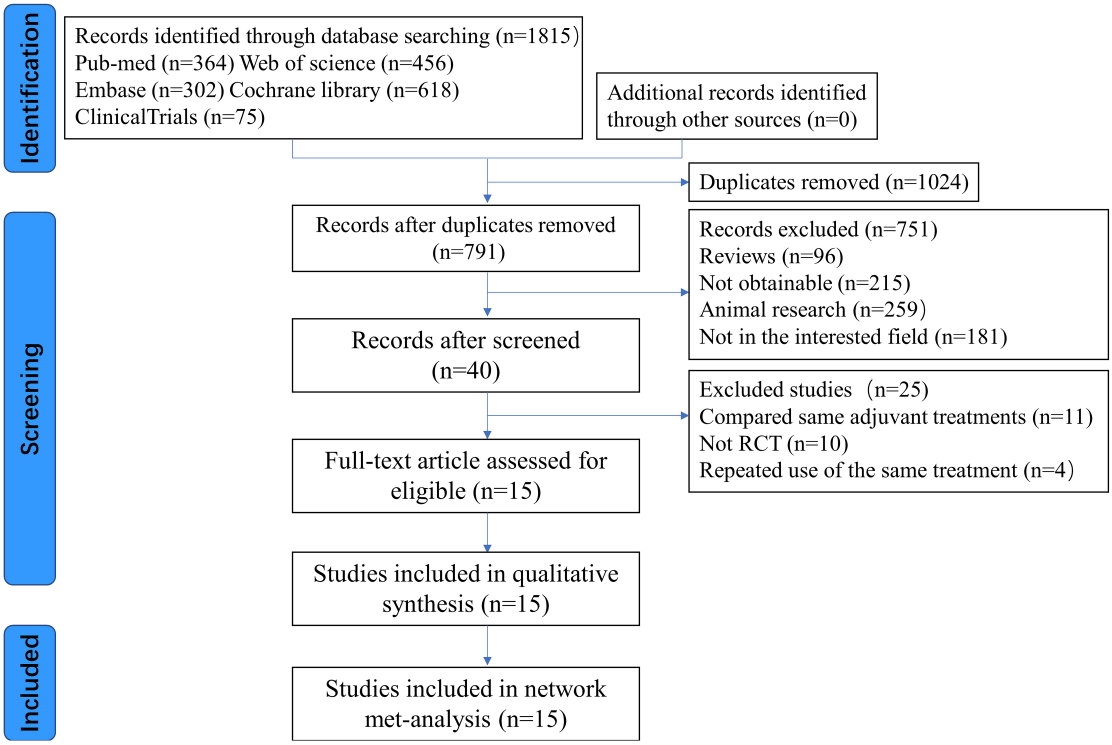

Fig. 1. Flow chart showing study selection. RCT, randomized clinical trial.

acid (ACP) was associated with lower IUA recurrence when compared with DBG (dried amnion graft or bone marrow stem cells-scaffold or granulocyte colony-stimulating factor) + Foley/HSB (OR = 0.22, 95% CI 0.06, 0.87), HSB (OR = 0.18, 95% CI 0.05, 0.67), Foley (OR = 0.14, 95% CI 0.03, 0.59), IUD (OR = 0.14, 95% CI 0.04, 0.48), and heart shape balloon or Foley 1 month (H/F) + IUD (OR = 0.10, 95% CI 0.02, 0.47), medical chitosan (MC) + IUD (OR = 0.08, 95% CI 0.01, 0.56); Foley + IUD was associated with lower IUA recurrence when compared with HSB (OR = 0.39, 95% CI 0.16, 0.95), Foley (OR = 0.30, 95% CI 0.10, 0.92), IUD (OR = 0.30, 95% CI 0.10, 0.89), and H/F + IUD (OR = 0.22, 95% CI 0.05, 0.90), MC + IUD (OR = 0.18, 95% CI 0.03, 0.93); ACP + Foley/IUD was associated with lower IUA recurrence when compared with HSB (OR = 0.53, 95% CI 0.31, 0.93), Foley (OR = 0.42, 95% CI 0.20, 0.87), IUD (OR = 0.41, 95% CI 0.19, 0.86), and H/F + IUD (OR = 0.30, 95% CI 0.09, 0.96), autologous platelet gel or platelet-rich plasma (APG/PRP) + IUD/HSB was associated with decreased IUA recurrence when compared with medical chitosan (MC) + IUD (OR = 0.28, 95% CI 0.10, 0.82). The SUCRA analysis showed comparable probability between the ten treatments (**Supplementary Fig. 4A**). Among the ten treatments according to the SUCRA rank, ACP and Foley + IUD (96.4% and 83.5%, respectively) had the highest mean ranks, whereas H/F + IUD and MC + IUD had the lowest mean ranks (16.6% and 13.5%, respectively).

The netleague analyses of clinical pregnancy are presented in Fig. 2. Dried amnion graft or bone marrow stem cells-scaffold or granulocyte colony-stimulating factor (DBG) + Foley/HSB was associated with increased clinical pregnancy when compared with HSB (OR = 2.11, 95% CI 1.34, 3.32). Foley + IUD, auto-cross-linked hyaluronic acid (ACP) + Foley/IUD, and IUD was associated with decreased clinical pregnancy when compared with heart shape balloon or Foley 1 month (H/F) + IUD (OR = 0.31, 95% CI 0.11, 0.87; OR = 0.14, 95% CI 0.03, 0.69; OR = 0.21, 95% CI 0.07, 0.59; respectively). The SUCRA analysis showed comparable probability between the eight treatments (**Supplementary Fig. 4B**). In addition, the SUCRA rank indicated that H/F + IUD and DBG + Foley/HSB (89.7% and 82.1%, respectively) had the highest mean ranks, whereas IUD and ACP + Foley/IUD had the lowest mean ranks (20.4% and 10.5%, respectively).

3.4 Inconsistency

Fitting the design-by-treatment interaction model did not provide evidence for inconsistent of the recurrence of IUA and clinical pregnancy (Global Wald test: $p = 0.229$; 0.476, respectively). **Supplementary Fig. 5** presents inconsistency plots for the recurrence of IUA, and we did not find any evidence of inconsistency. Owing to the small number of studies on clinical pregnancy, we could not perform inconsistency plots for this outcome. In addition, we cannot exclude the possibility that the actual number of inconsistent loops is higher than the number we reported.

	Clinical Pregnancy									
IUA Recurrence	**ACP**	1.45 (0.34,6.21)	3.32 (0.98,11.25)	0.97 (0.15,6.07)	0.62 (0.12,3.39)	1.32 (0.26,6.71)	NA	2.19 (0.78,6.10)	3.32 (0.98,11.25)	NA
	0.47 (0.10,2.27)	**Foley + IUD**	2.29 (0.46,11.35)	0.67 (0.22,2.05)	0.43 (0.18,1.02)	0.91 (0.43,1.90)	NA	1.50 (0.54,4.21)	**0.31 (0.11,0.87)**	NA
	0.34 (0.09,1.24)	0.73 (0.25,2.08)	**ACP + Foley/IUD**	0.29 (0.04,2.06)	0.19 (0.03,1.16)	0.40 (0.07,2.31)	NA	0.66 (0.19,2.25)	**0.14 (0.03,0.69)**	NA
	0.30 (0.06,1.44)	0.64 (0.18,2.25)	0.88 (0.31,2.50)	**APG/PRP + IUD/HSB**	0.65 (0.25,1.69)	1.36 (0.58,3.18)	NA	2.26 (0.49,10.38)	0.47 (0.10,2.14)	NA
	0.22 (0.06,0.87)	0.47 (0.17,1.28)	0.65 (0.33,1.27)	0.74 (0.27,1.99)	**DBG + Foley/HSB**	**2.11 (1.34,3.32)**	NA	3.50 (0.91,13.43)	0.72 (0.19,2.78)	NA
	0.18 (0.05,0.67)	**0.39 (0.16,0.95)**	**0.53 (0.31,0.93)**	0.61 (0.25,1.47)	0.82 (0.52,1.29)	**HSB**	NA	1.66 (0.47,5.88)	0.34 (0.10,1.22)	NA
	0.14 (0.03,0.59)	**0.30 (0.10,0.92)**	**0.42 (0.20,0.87)**	0.47 (0.16,1.42)	0.64 (0.29,1.43)	0.78 (0.41,1.50)	**Foley**	NA	NA	NA
	0.14 (0.04,0.48)	**0.30 (0.10,0.89)**	**0.41 (0.19,0.86)**	0.46 (0.16,1.38)	0.63 (0.29,1.37)	0.76 (0.40,1.44)	0.98 (0.41,2.36)	**IUD**	**0.21 (0.07,0.59)**	NA
	0.10 (0.02,0.47)	**0.22 (0.05,0.90)**	**0.30 (0.09,0.96)**	0.34 (0.08,1.40)	0.47 (0.14,1.52)	0.57 (0.19,1.69)	0.72 (0.21,2.53)	0.74 (0.30,1.80)	**H/F + IUD**	NA
	0.08 (0.01,0.56)	**0.18 (0.03,0.93)**	0.25 (0.06,1.10)	**0.28 (0.10,0.82)**	0.38 (0.09,1.64)	0.46 (0.12,1.85)	0.59 (0.13,2.74)	0.61 (0.13,2.79)	0.82 (0.14,4.79)	**MC + IUD**

Fig. 2. The netleague analyses of IUA recurrence and clinical pregnancy. The comparisons of data are odds ratios (95% confidence interval), which should be read from left to right. ORs higher than 1 favor the left treatments, lower than 1 favor the right treatments. Significant results are in bold and underline. IUA, Intrauterine Adhesion; ACP, Auto-cross-linked Hyaluronic Acid; Foley, Foley balloon catheter; IUD, Intrauterine Device; APG, Autologous Platelet Gel; PRP, Platelet-Rich Plasma; DBG, Dried Amnion Graft or Bone Marrow Stem Cells-scaffold or Granulocyte Colony-Stimulating Factor; HSB, Heart Shape Balloon; H/F, Heart Shape Balloon or Foley; MC, Medical Chitosan; NA, Not available.

3.5 Secondary Outcomes

All our secondary outcomes were infrequently reported. Two RCTs reported on menstrual blood volume, and three RCTs reported on second-look IUA score. Consequently, network meta-analysis was not performed for secondary outcomes. The results of pairwise meta analyses were presented in **Supplementary Fig. 6** and showed that dried amnion graft or bone marrow stem cells scaffold or granulocyte colony-stimulating factor (DBG) + Foley/HSB may increase menstrual blood volume (mean difference (MD) = 1.06, 95% CI 0.70, 1.41). There are insufficient studies on the second-look IUA score to perform relevant pairwise meta-analyses.

3.6 Small Study Effects

Overall, we found no strong evidence of the influence of small study effects across results, and the symmetrical funnel diagram (**Supplementary Fig. 7A,B**) showed that there was no significant publication bias about the recurrence of IUA and clinical pregnancy in our meta-analysis.

4. Discussion

This systematic review and network meta-analysis of treatments to reduce the recurrence of IUAs and improve pregnancy outcome after hysteroscopic adhesiolysis included data from 15 RCTs involving 1827 patients who were randomized to ten distinct treatment protocols. The quality of evidence was all low risk of bias. However, the results should be interpreted with caution because they were based on open-loop networks partly.

The AAGL Practice Guidelines for Management of Intrauterine Synechiae highlight that direct visualization of the uterine cavity at hysteroscopy in conjunction with a tool for adhesiolysis is an effective technique for the lysis of

IUAs [3]. Owing to the high recurrence rate of postoperative adhesions and low pregnancy rate, use of a physical barrier to prevent IUA formation and promote intimal recovery after the operation is a hot topic in the field. Auto-cross-linked hyaluronic acid (ACP) is often used to prevent postoperative tissue adhesion because of its unique biocompatibility and enzymatic biodegradation [28]. A study by Vitale found that an intrauterine Foley catheter (46.4%) or ACP (21.3%) were potentially the most effective methods for avoiding IUA recurrence after the hysteroscopic lysis of adhesions [29]. Similarly, we found intrauterine ACP (96.4%) or Foley + IUD (83.5%) may be the most effective treatment approaches. Besides, the study of Vitale only included eleven studies with 1596 patients, using eight distinct treatment protocols. In the study of Yan, patients were with or at high risk of developing IUA, they are not fully IUA, and only six studies described adjuvant therapies in IUA patients [30]. But our research had expanded the number of included studies, patients, and treatment methods. There are fifteen RCT studies with 1827 patients, utilizing ten distinct treatment protocols. The results of our research can better reflect the ongoing research level and present more helpful evidence for the clinical decision-making.

Endometrial recovery after transcervical resection of adhesion takes at least one month, thus the treatment of heart shape balloon or Foley 1 month (H/F) + IUD can provide enough time for the endometrial recovery, which may play a crucial role in increasing clinical pregnancy after the procedure [31]. Reducing fibrosis is only part of the process for endometrial recovery; angiogenesis and stem cell homing may be other explanations for the increase in clinical pregnancy [32]. The role in endometrial recovery may explain why H/F + IUD can improve clinical pregnancy but is not ideal for reducing IUA recurrence. Further research is needed to confirm this theory. Following H/F + IUD, the next most successful treatment for improving clinical pregnancy is dried amnion graft or bone marrow stem cells-scaffold or granulocyte colony-stimulating factor (DBG) + Foley/HSB. Bone marrow mesenchymal stem cells can promote endometrial regeneration and reverse endometrial stromal transformation through the Wnt/β-catenin signaling pathway, and reverse epithelial mesenchymal transition through the transforming growth factor (TGF)-β1/Smad pathway to promote the repair of damaged endometrium [33,34]. In addition, the amniotic membrane promotes endometrial regeneration as a source of stem cells [22,35]. Bone marrow mesenchymal stem cells and the amniotic membrane both advance endometrial recoveries, thus achieving the possibility of clinical pregnancy [36,37]. G-CSF stimulates decidual macrophages, mediates the transformation of Th1/Th2 ratio to Th2 response, promotes an increase of regulatory T cells, and improves implantation through rolling, apposition, adhesion, and invasion [12,38], which promote clinical pregnancy. Furthermore, for patients with only a thin endometrium maybe with stem cell homing disorder, further clinical and basic research is required to confirm whether DBG + Foley/HSB can improve pregnancy outcomes in these patients.

Our research has many limitations. First, for IUA patients with fertility needs, preventing adhesion formation and promoting endometrial recovery after hysteroscopic adhesiolysis are the basis of pregnancy. Recent researches show that dried amnion graft, stem cells, or G-CSF can promote endometrial regeneration and recovery to achieve the possibility of clinical pregnancy [10,12,13,32]. However, because there are limited studies on these methods, and the methods all promote pregnancy directly or via endometrium recovery, our research combined these approaches into one treatment method, combining the approaches may have masked the specific roles of the individual treatments. Besides, autologous platelet gel or platelet-rich plasma (APG/PRP) has also been studied for endometrium regeneration [8], also for the lack of related studies, the influence of APG/PRP on IUA is not clear. Additional research is urgently needed to confirm the specific role of amnion graft, stem cells, G-CSF, and APG/PRP since they can not only repair endometrium, but also improve the endometrial microenvironment by increasing vascularization or immunomodulatory effects in mechanism [12,35,39,40]. Second, there are too few data about menstrual flow and second-look IUA score in published studies to conduct further analyses. Third, most studies have not been stratified according to mild, moderate, or severe IUA; the inconsistency of surgical instruments may influence the postoperative treatment effects; and different follow-up times may affect the judgment of pregnancy outcome index. In the future, more RCT studies with careful design for different factors should be conducted.

5. Conclusions

For patients with IUA that have undergone hysteroscopic adhesiolysis, DBG + Foley/HSB may increase clinical pregnancy compared with the control according to our pairwise meta-analysis. ACP and Foley + IUD may be suitable alternatives to reduce IUA recurrence, H/F + IUD and DBG + Foley/HSB may be associated with an increased clinical pregnancy rate according to our network meta-analysis. However, these results should be interpreted with caution because they were based on small studies and open-loop network analysis partly. There is insufficient evidence regarding secondary outcomes of the treatment options. More RCTs about DBG + Foley/HSB needs to be designed, the relative effectiveness of different degrees of IUA treatment should be further clarified, and more attention should be paid to clinical pregnancy, menstrual blood volume and second-look IUA score.

Availability of Data and Materials

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

Author Contributions

LJL, XYQ and HC designed the research study. LJL and XYQ performed the research and collected the data. LZX and XPC provided help and advice to LJL, XYQ and HC. LJL, XYQ and XPC analyzed the data. LJL, XYQ and HC wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5104102.

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