

## ARTICLE

# A Network Meta-Analysis of Efficacy of Different Interventions in the Prevention of Postoperative Intrauterine Adhesions

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This network meta-analysis was conducted to compare the efficacy of six interventions, including anti-blocking agents, intrauterine contraceptive devices (IUDs), estrogens, intrauterine balloon, Foley catheter, and amnion graft for the prevention of intrauterine adhesions (IUAs). We searched PubMed, Embase, and Cochrane Library from inception to December 2016. Cohort studies meeting these six interventions in the prevention of IUAs were included. The combination of direct and indirect evidence was conducted to assess the odds ratio (OR) or weighted mean differences and surface under the cumulative ranking curves of the six interventions in the prevention of postoperative IUAs. Finally, 12 eligible cohort studies were included in this network meta-analysis. The results of this network meta-analysis demonstrated that during 1 to 2 months after operation, compared with the surgical group, anti-blocking agent, and estrogens presented with relatively low ratios of postoperative IUAs (OR = 0.30 95% confidence interval (CI) = 0.10–0.67; OR = 0.12, 95% CI = 0.01–0.78, respectively). Compared with IUDs, estrogens exerted comparatively low ratio of postoperative IUAs (OR = 0.10, 95% CI = 0.01–0.90), which indicated that anti-blocking agent and estrogens had relatively better prevention efficacy. The cluster analysis showed that estrogens had relatively better efficacy in the prevention postoperative IUAs. Overall, our findings support that estrogens had relatively better efficacy in the prevention of postoperative IUAs.

## Study Highlights

### WHAT IS THE CURRENT KNOWLEDGE ON THIS TOPIC?

☑ Intrauterine adhesions (IUAs) are often commonly produced following intrauterine surgery, and despite comprehensive measures being undertaken to prevent the occurrence of IUAs, some severe endometrial injuries are inevitable.

### WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Currently, the best choice for prevention of postoperative IUAs remains to be a controversial issue with no answer in sight. Therefore, this study compared the efficacy of six interventions, including anti-blocking agents,

intrauterine contraceptive devices, estrogens, intrauterine balloons, Foley catheters, and amnion grafts for the prevention of IUAs.

### WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Estrogens may be the best choice among these six interventions for the prevention of postoperative IUAs.

### HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Our network meta-analysis provides a new insight for the prevention of postoperative IUAs with estrogens as target.

Intrauterine adhesions (IUAs), also known as Asherman syndrome, are a serious complication that can arise after a miscarriage and intrauterine surgery, and are associated with secondary infertility and severe obstetric complications.<sup>1,2</sup> IUAs develop following the destruction of the basal layer of the endometrium, arising in as many as 30% women undergoing postpartum uterine apoxesis.<sup>2</sup> It has been estimated that the prevalence of Asherman syndrome ranges from 2.84–5.5% in women with abnormal menstruation and reproductive failures, and the possible potential causes of IUAs include dilation and curettage, especially in a gravid

uterus.<sup>4</sup> The category of possible fertility symptoms in patients with IUAs includes secondary infertility and recurrent miscarriages, ectopic pregnancy, abnormal placentation, fetal growth restriction, fetal anomalies, premature delivery, and postpartum hemorrhage.<sup>2</sup> Patients with unacceptable pain or menstrual dysfunction will accept treatment, and it is more common that patients will accept treatment when they have a history of infertility or recurrent pregnancy loss wish to conceive.<sup>5</sup>

To prevent the occurrence of IUAs, several interventions were invented and improved by investigators. In the past,

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the insertion of an intrauterine contraceptive device (IUD) was a widely used method to prevent adhesions, and recently, the copper-containing IUDs and hormonal IUDs are also applied in different situations.<sup>6</sup> Another key intervention, the Foley catheter, is also inserted into the uterine cavity after hysteroscopic surgery to prevent recurrence of IUAs.<sup>7</sup> Similarly, the use of an intrauterine balloon with a triangular shape that can conform completely to the configuration of a uterine cavity and sustain separation at the margins of the uterine cavity is also commonly applied in the prevention of IUAs.<sup>8</sup> Furthermore, estrogen is often used to promote endometrial proliferation and healing after surgery.<sup>9</sup> With the development of regenerative medicine, like cell therapy, there is a potential to treat IUAs with low recurrence rate.<sup>10</sup> A study supported the argument that intrauterine balloon stents are relatively safer than tailed IUDs.<sup>11</sup> Amnion graft was found to be a promising treatment for its inhibition of infection, fibrosis, and adhesion reformation.<sup>12</sup> The use of anti-blocking agents, such as auto-cross-linked hyaluronic acid (ACP) gel and polyethylene oxide-sodium carboxymethylcellulose gel, has also been found to be effective in the prevention of postoperative IUAs.<sup>13,14</sup> In addition, another study reported high success rates of hysteroscopic adhesiolysis in the prevention of spontaneous recurrence of IUAs in patients with Asherman syndrome.<sup>15</sup> However, previous evidence indicates that the recurrence rate of IUAs after hysteroscopic adhesiolysis is as high as 30–60%.<sup>16,17</sup> Considering the heterogeneity in the risk of adhesion formation, when we analyzed the adhesion scores, we used the difference before and after the intervention, which greatly reduced the bias of the results caused by the difference of the condition of the subjects.

Currently, there remains to be no comprehensive diagnosis for the efficacy of different interventions to prevent postoperative IUAs.<sup>7</sup> Thus, in the current study, we aim to apply a network meta-analysis, which allows the integration of data from direct and indirect comparisons, to compare the efficacy of six interventions in the prevention of postoperative IUAs. Simultaneously, we aim to provide a clinically useful summary of results of the multiple-treatments meta-analysis that can be used to effectively guide treatment decisions in the future.

## MATERIALS AND METHODS

### Search strategy

PubMed, Embase, Cochrane Library, and other English language databases were searched from the inception of each database to December 2016. In addition, manual searches were performed for the relevant references and all references in the included studies. The search criteria included a combination of the following keywords and free words: Asherman Syndrome, gynaesmia, uterine adhesion, cervical adhesion, intrauterine adhesions, hysteroscopic adhesiolysis, hysteroscopic septal resection, myomectomy, Interceed, anti-blocking agent, hyaluronic acid gel, ACP gel, Seprafilm, intrauterine contraceptive device, IUD, intrauterine device, estrogens, intrauterine balloon, Foley catheter, balloon catheter, fresh amnion graft, randomized controlled study, randomized controlled studies (RCTs), and cohort study.

### Inclusion and exclusion criteria

The inclusion criteria were as follows: (i) study design: RCTs or cohort studies; (ii) interventions: anti-blocking agent, IUD, estrogens, intrauterine balloon, Foley catheter (rounded balloon) and amnion graft; (iii) study subjects: female patients aged 20–45 years who underwent polypectomy, metroplasty, endometrial ablation, hysteroscopic lysis or uterine myomectomy, and had a risk of postoperative IUAs; (iv) outcomes: adhesion rate or adhesion score (adhesions were examined by second hysteroscopy 1–2 months after operation, and the difference between the adhesion score before and after intervention was subjected to a subsequent statistical analysis). The exclusion criteria were as follows: (i) patients with presence of any other known reasons for infertility or abortion; (ii) patients with contraindication hormone therapy; (iii) patients with acute cervicitis; (iv) insufficient data integrity (e.g., non-paired studies); (v) non-cohort study and non-randomized controlled study; (vi) duplicated publications; (vii) conference reports, systematic reviews or abstract articles; and (viii) non-English studies.

### Data extraction and quality assessment

Firstly, data were independently extracted from the enrolled studies using a uniformly designed form by two reviewers. An additional third reviewer was consulted if agreement could not be reached between the two reviewers. Two or more researchers assessed the study quality in accordance with the Newcastle-Ottawa Scale (NOS),<sup>18</sup> and the standards of NOS were as follows: (i) cohort selection: good representativeness of the exposed cohort (NOS1), nonexposed cohort drawn from the same community with exposed cohort or a different source (NOS2), secure record or structured interview (NOS3), demonstration that outcomes of interest were not present at the start of study (NOS4); (ii) cohort comparability: study controls for selecting the most important factors (NOS5), study controls for any additional factor (NOS6); (iii) cohort outcome: independent and blind assessment (NOS7); sufficient follow-up time for outcomes to occur (NOS8); and completion of follow-up on all subjects or a small number of subjects lost to follow-up unlikely to introduce bias (NOS9). The total scores of NOS were nine points, and studies with more than five points were included in the current meta-analysis.

### Statistical analysis

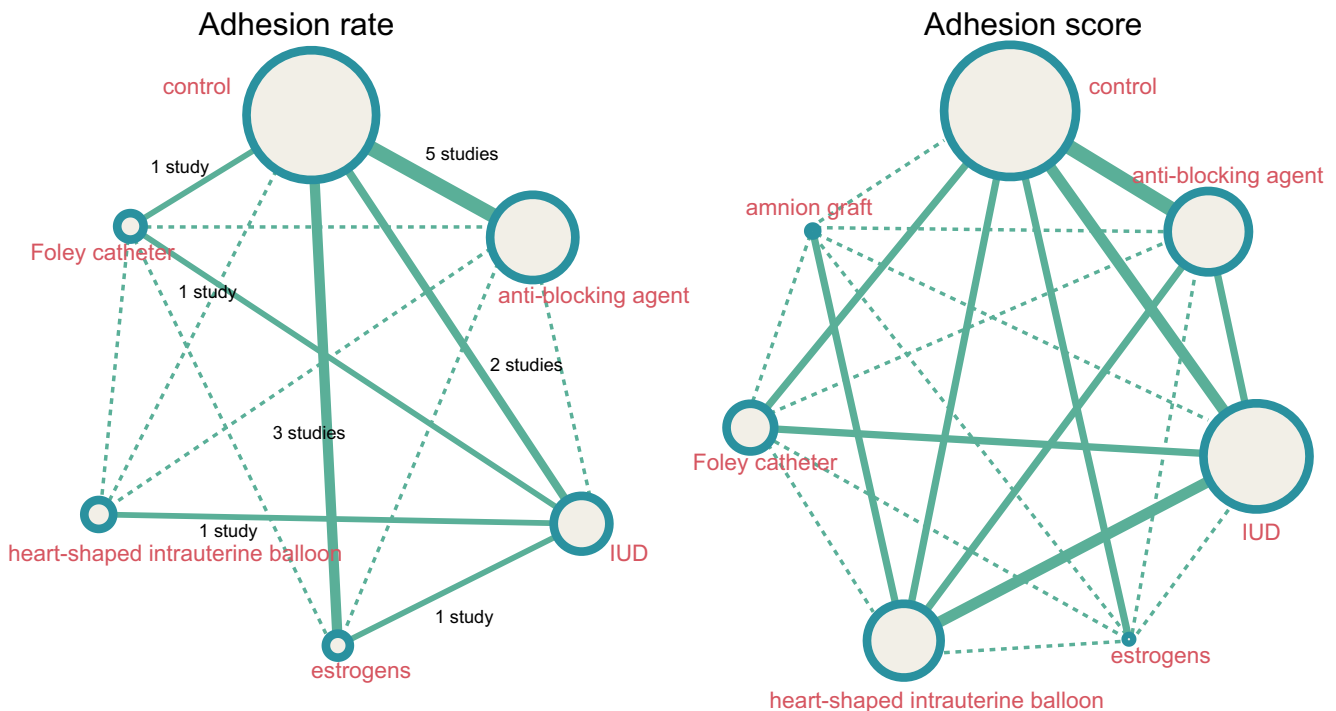
First, traditional pairwise meta-analyses were performed to directly compare six different interventions (anti-blocking agents, IUDs, estrogens, intrauterine balloon, Foley catheter, and amnion graft) for the prevention of postoperative IUAs. We reported the pooled estimates of the odds ratio (OR)/weighted mean difference (WMD) and 95% confidence intervals (CIs). In order to test heterogeneity, we applied the  $\chi^2$  test and I-square test among the included studies.<sup>19</sup> In addition, Bayesian network meta-analyses were performed to compare six different interventions (anti-blocking agents, IUDs, estrogens, intrauterine balloon, Foley catheter, and amnion graft) for the prevention of postoperative IUAs. Each analysis was based on noninformative priors for effect sizes

and precision. Convergence and lack of autocorrelation were checked and confirmed after four chains and a 20,000-simulation burn-in phase. Eventually, direct probability statements were derived from an additional 50,000-simulation phase.<sup>20</sup> The R software is free software with powerful data processing and graphics rendering. The application R software in the meta-analysis is very mature and widespread, which can be realized through the packages such as meta, metafor, and metaplan (the R software running code used in the present study was determined by the data statistics expert after multiple verifications). The R version 3.2.1 software was used to draw the network evidence diagram, in which each node represents an intervention, the node size represents the sample size, and the line thickness between nodes represents the number of included studies. The node-splitting method was used to assess the consistency between direct and indirect evidence, and the selection of the consistency or inconsistency model was based on these results, whereas the consistency model was applied if  $P > 0.05$ .<sup>21</sup> Surface under the cumulative ranking curve (SUCRA) values were used to calculate the probability of each intervention being the most effective treatment method based on a Bayesian approach using probability values, and the larger the SUCRA value, the better the rank of the intervention.<sup>22,23</sup> Additionally, cluster analyses were carried out to evaluate the effectiveness of different interventions for the prevention of postoperative IUAs, which is based on two variable similarities to cluster the merits of different interventions and to determine their effectiveness in the prevention of postoperative IUAs.<sup>22</sup> All computations were performed using the R version 3.2.1 package gemtc software version 0.6, along with the Markov Chain Monte Carlo engine Open BUGS version 3.4.0.

**RESULTS**

**Baseline characteristics of included studies**

Our electronic database searches yielded a total of 2,544 candidate studies. After reviewing the titles and abstracts, we excluded 156 duplicate studies, 687 letters or summaries, 269 nonhuman studies, and 302 non-English studies. Upon further assessment of the remaining 1,130 articles, we excluded an additional 295 noncohort studies and non-RCTs, 812 studies without interventions for prevention of postoperative IUAs, and 2 studies without data resources or with incomplete documentation. Eventually, a sum of 10 cohort studies and two RCTs published between 1996 and 2016 were deemed eligible for this network meta-analysis<sup>4,13,14,24,25</sup> (Figure S1). These 12 cohort studies included 1,154 patients with risks of postoperative IUAs undergoing hysteroscopic transection, hysteroscopic septal resection, hysteroscopic adhesiolysis, or myomectomy, of which anti-blocking agents and IUDs were comparatively often used in the prevention of postoperative IUAs (Figure 1; the circle size is indicative of sample size and the larger the circle, the larger the sample size). Among the included studies, six studies included white subjects, five studies with Asian subjects, one study with African subjects, one study was four-arm trial, two were three-arm trails, and the remaining nine were two-arm trails. Baseline characteristics of the included studies are summarized in Table 1. The NOS risk of bias assessment of included studies is shown in Figure S2. Most of the included studies presented with low risk of bias, a few unclear, and a few with high risk of bias. Overall, the quality of the included literature was well above average and satisfactory.



**Figure 1** Network evidence diagram for different interventions in the prevention of postoperative intrauterine adhesions. IUD, intrauterine contraceptive device.

Table 1 The baseline characteristics for included studies

First author	Year	Country	NOS score	Surgery	Interventions				Sample size				Age (years)				
					T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4	
					Total	T1	T2	T3	T4	T1	T2	T3	T4	T1	T2	T3	T4
Yu X	2016	China	8	Hysteroscopic transection	A	C	F	-	188	54	59	75	-	31.7 ± 4.5	31.3 ± 5.1	31.1 ± 4.3	-
Lin XN	2015	China	6	Hysteroscopic adhesiolysis	C	E	-	-	162	80	82	-	-	30.1 ± 5.1	29.7 ± 4.3	-	-
Roy KK	2014	India	8	Hysteroscopic septal resection	A	D	-	-	90	45	45	-	-	27.3 ± 3.9	28.7 ± 4.8	-	-
Lin X	2013	China	7	Hysteroscopic adhesiolysis	A	B	C	E	107	41	18	28	20	31.2 ± 4.3	31.3 ± 4.5	29.8 ± 5.4	29.0 ± 2.4
Di Spiezio Sardo A	2011	Italy	7	Myomectomy/Polypectomy/Metroplasty/Endometrial ablation	A	B	-	-	110	55	55	-	-	36 ± 2.9	37 ± 3.1	-	-
Tonguc EA	2010	Turkey	6	Hysteroscopic uterine septum resection	A	C	D	-	100	25	25	25	-	26.95 ± 4.90	27.05 ± 4.66	27.25 ± 4.30	-
Amer MI	2010	Egypt	8	Hysteroscopic lysis	E	G	-	-	28	14	14	-	-	30.5 (27-34)	31.5 (29-35)	-	-
Guida M	2004	Italy	8	Hysteroscopic adhesiolysis	A	B	-	-	132	65	67	-	-	36 ± 2.8	37 ± 3.2	-	-
Pellicano M	2003	Italy	7	Laparoscopic myomectomy	A	B	-	-	36	18	18	-	-	30.7 ± 2.6	28.8 ± 4.1	-	-
Imai A	2003	Japan	7	Myomectomy	A	D	-	-	15	5	10	-	-	32.6 ± 3.29	31.2 ± 5.53	-	-
Acunzo G	2003	Italy	6	Hysteroscopic adhesiolysis	A	B	-	-	84	41	43	-	-	30.7 ± 2.6	29.8 ± 4.1	-	-
Diamond MP	1996	America	8	Uterine myomectomy	A	B	-	-	127	68	59	-	-	34.7 ± 5.1	34.8 ± 5.1	-	-

A, control; B, anti-blocking agent; C, intrauterine contraceptive device; D, estrogens; E, intrauterine balloon; F, Foley catheter; G, amnion graft; NOS, Newcastle-Ottawa Scale; T, treatment.

**Pairwise meta-analysis for efficacy of six interventions in the prevention of postoperative IUAs**

Compared with the control, anti-blocking agent and estrogens presented with lower ratio of postoperative IUAs (OR = 0.33, 95% CI = 0.21-0.53; and OR = 0.11, 95% CI = 0.02-0.68, respectively) during 1-2 months after operation, indicating that anti-blocking agents and estrogens exhibited better preventive efficacy. Estrogens and intrauterine balloons presented with lower postoperative adhesion scores compared with the control (WMD = -1.80, 95% CI = -2.71 to -0.89; and WMD = -3.00, 95% CI = -4.08 to -1.92, respectively). Compared with anti-blocking agents, the postoperative adhesion scores of IUDs and intrauterine balloons were determined to be relatively low (WMD = -5.50, 95% CI = -6.54 to -4.46; and WMD = -5.50, 95% CI = -6.75 to -4.25, respectively). Compared with intrauterine balloons, amnion grafts exhibited lower postoperative adhesion score (WMD = -0.50, 95% CI = -0.60 to -0.40; **Table 2**).

**Inconsistency test of network meta-analysis for efficacy of six interventions in the prevention of postoperative IUAs**

The inconsistency tests of adhesion rate and adhesion score were performed by the node-splitting method. The results revealed consistency among the studies in terms of the results of the direct and indirect evidence of all outcomes (all *P* > 0.05). Therefore, the consistency model was applied for further analyses (**Figure 2**).

**Main results of network meta-analysis for efficacy of six interventions in the prevention of postoperative IUAs**

The results of the current study demonstrated that during 1-2 months after operation, anti-blocking agents and estrogens presented with relatively lower ratio of postoperative IUAs compared with the control (OR = 0.30; 95% CI = 0.10-0.67; OR = 0.12, 95% CI = 0.01-0.78, respectively). Compared with IUDs, estrogens exhibited comparatively lower ratio of postoperative IUAs (OR = 0.10, 95% CI = 0.01-0.90), indicating that anti-blocking agents and estrogens exerted better preventive efficacy in the treatment of postoperative IUAs. However, in regard to adhesion score, there were no significant differences in the preventive efficacy of each intervention (**Figure 3 and Table 3**).

**SUCRA values of efficacy of six interventions in the prevention of postoperative IUAs**

The SUCRA values of the interventions for the prevention of postoperative IUAs are summarized in **Figure 4**. The results indicated that, in terms of adhesion rate, estrogens presented with the highest SUCRA value (94.00%), followed by anti-blocking agents (83.67%). In terms of adhesion score, intrauterine balloons and amnion grafts exhibited the highest SUCRA values of 73.86% and 73.43%, respectively.

**Cluster analysis for adhesion rate and adhesion score**

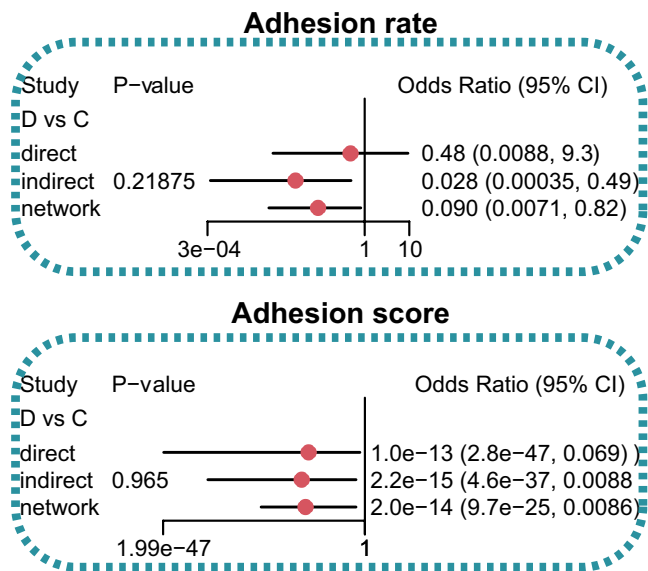
Finally, a cluster analysis was applied to unearth the best intervention for the prevention of postoperative IUAs. The results of the cluster analysis for adhesion rate and adhesion

**Table 2** Estimated OR/WMD and 95% CI from pairwise meta-analysis in terms of adhesion rate and adhesion score

Included studies	Comparisons	Pairwise meta-analysis		
		OR/WMD (95% CI)	I <sup>2</sup>	P <sub>h</sub>
5 studies	B vs. A	<b>0.33 (0.21–0.53)</b>	0%	0.4480
2 studies	C vs. A	1.34 (0.61–2.98)	0%	0.7059
3 studies	D vs. A	<b>0.11 (0.02–0.68)</b>	0%	0.5225
1 study	F vs. A	1.15 (0.51–2.57)	NA	NA
1 study	D vs. C	0.21 (0.01–4.76)	NA	NA
1 study	E vs. C	0.81 (0.42–1.57)	NA	NA
1 study	F vs. C	0.90 (0.42–1.92)	NA	NA
3 studies	B vs. A	0.52 (–3.31–4.35)	98.5%	< 0.0001
2 studies	C vs. A	–1.48 (–4.42–1.46)	97.5%	< 0.0001
1 study	D vs. A	<b>–1.80 (–2.71 to –0.89)</b>	NA	NA
1 study	E vs. A	<b>–3.00 (–4.08 to –1.92)</b>	NA	NA
1 study	F vs. A	–0.10 (–0.51–0.31)	NA	NA
1 study	C vs. B	<b>–5.50 (–6.54 to –4.46)</b>	NA	NA
1 study	E vs. B	<b>–5.50 (–6.75 to –4.25)</b>	NA	NA
2 studies	E vs. C	0.00 (–0.68–0.68)	NA	NA
1 study	F vs. C	–0.10 (–0.48–0.28)	NA	NA
1 study	G vs. E	<b>–0.50 (–0.60 to –0.40)</b>	NA	NA

The use of bold indicates significant difference.

95% CI, 95% confidence interval; A, control; B, anti-blocking agent; C, intrauterine contraceptive device; D, estrogens; E, intrauterine balloon; F, Foley catheter; G, amnion graft; NA, not available; OR, odds ratios; WMD, weighted mean difference.



**Figure 2** Node-splitting diagram for different interventions in the prevention of postoperative intrauterine adhesions (A = control; B = anti-blocking agent; C = intrauterine contraceptive device; D = estrogens; E = intrauterine balloon; F = Foley catheter; and G = amnion graft). CI, confidence interval.

score demonstrated that estrogens were relatively better in the prevention of postoperative IUAs (**Figure S3**).

**DISCUSSION**

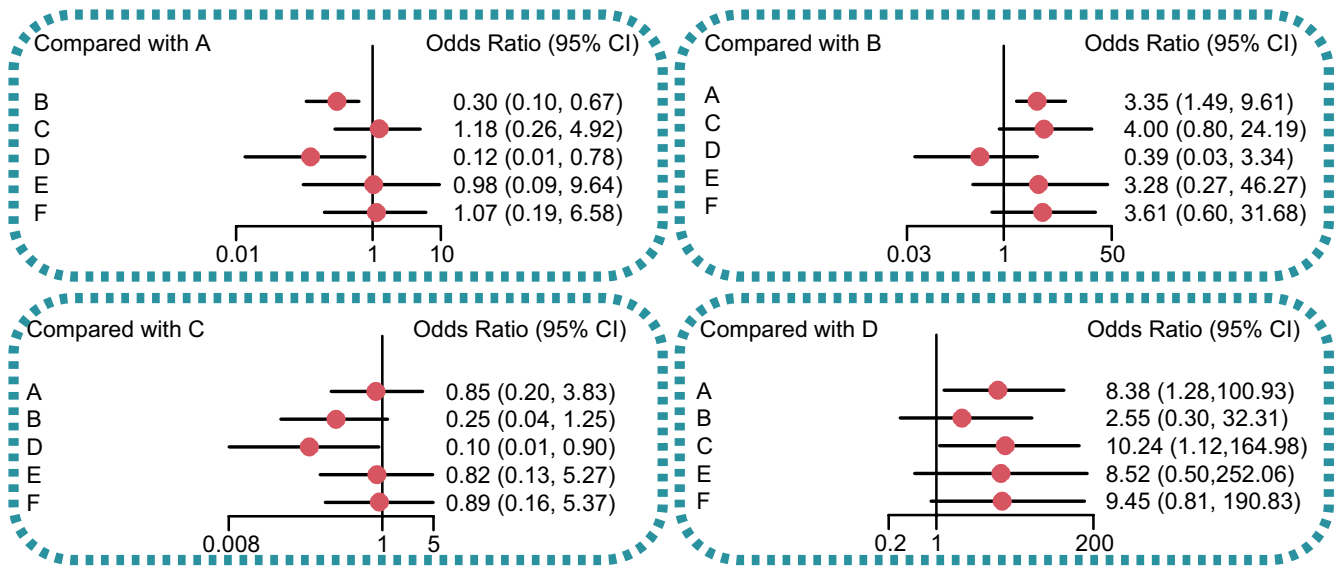
Joseph G.A Sherman described the syndrome of IUAs, which has borne his name ever since.<sup>33</sup> In his original

description, he stated that traumatic IUAs did not necessarily result in menstrual disturbances.<sup>34</sup> The presence of IUAs may contribute to various unfortunate conditions, such as infertility, miscarriage, as well as a number of obstetric complications.<sup>35</sup> IUAs are often commonly produced following intrauterine surgery, and despite comprehensive measures being undertaken to prevent the occurrence of IUAs, some severe endometrial injuries are inevitable.<sup>36</sup> Currently, the best choice for prevention of postoperative IUAs remains to be a controversial issue with no answer in sight. Hence, we conducted this network meta-analysis to compare the efficacy of anti-blocking agents, IUDs, estrogens, intrauterine balloons, Foley catheters, and amnion grafts in the prevention of postoperative IUAs, and we discovered that estrogens may be the best choice among these six interventions for the prevention of postoperative IUAs.

First, we performed a pairwise meta-analysis to directly compare the six different interventions, and found that anti-blocking agents and estrogens presented with lower ratios of postoperative IUAs compared with the control; estrogens and intrauterine balloons exhibited lower adhesion scores. There have been some clinical studies that compared the curative effect of different intervention methods after different operation to prevent the postoperative IUAs (including the elimination of special cases and the patients with poor operation effect), and that drew clear conclusions that were of great value. For instance, in 2003, Acunzo et al. highlighted that intrauterine application of ACP gel after hysteroscopic adhesiolysis significantly prevented and reduced the development of *de novo* postoperative IUAs.<sup>31</sup> Meanwhile, a previous meta-analysis assessed the efficacy of IUDs as an adjunctive treatment modality for IUAs, and suggested the use of IUDs was beneficial in patients



### Adhesion rate



**Figure 3** Relative forest plots for different interventions on the incidence of postoperative intrauterine adhesions (A = control; B = anti-blocking agent; C = intrauterine contraceptive device; D = estrogens; E = intrauterine balloon; and F = Foley catheter). CI, confidence interval.

**Table 3** OR/WMD and 95% CIs of nine treatment modalities of two end point outcomes

OR/WMD (95% CI)							
Adhesion rate							
<b>A</b>	<b>0.30 (0.10, 0.67)</b>	1.18 (0.26, 4.92)	<b>0.12 (0.01, 0.78)</b>	0.98 (0.09, 9.64)	1.07 (0.19, 6.58)		
<b>3.35 (1.49, 9.61)</b>	<b>B</b>	4.00 (0.80, 24.19)	0.39 (0.03, 3.34)	3.28 (0.27, 46.27)	3.61 (0.60, 31.68)		
0.85 (0.20, 3.83)	0.25 (0.04, 1.25)	<b>C</b>	<b>0.10 (0.01, 0.90)</b>	0.82 (0.13, 5.27)	0.89 (0.16, 5.37)		
<b>8.38 (1.28, 100.93)</b>	2.55 (0.30, 32.31)	<b>10.24 (1.12, 164.98)</b>	<b>D</b>	8.52 (0.50, 252.06)	9.45 (0.81, 190.83)		
1.03 (0.10, 10.64)	0.30 (0.02, 3.65)	1.22 (0.19, 7.48)	0.12 (0.00, 1.99)	<b>E</b>	1.11 (0.09, 14.87)		
0.93 (0.15, 5.27)	0.28 (0.03, 1.66)	1.13 (0.19, 6.20)	0.11 (0.01, 1.24)	0.90 (0.07, 11.12)	<b>F</b>		
Adhesion score							
<b>A</b>	-0.33 (-4.12, 3.72)	-2.68 (-7.11, 1.96)	-1.79 (-8.78, 5.09)	-3.36 (-8.82, 2.03)	-1.45 (-7.92, 4.93)	-3.92 (-12.88, 4.97)	
0.33 (-3.72, 4.12)	<b>B</b>	-2.36 (-7.47, 2.79)	-1.48 (-9.45, 6.28)	-3.00 (-8.99, 2.62)	-1.10 (-8.39, 5.90)	-3.54 (-12.90, 5.27)	
2.68 (-1.96, 7.11)	2.36 (-2.79, 7.47)	<b>C</b>	0.88 (-7.28, 8.93)	-0.72 (-5.58, 4.18)	1.22 (-5.38, 7.63)	-1.23 (-9.90, 7.37)	
1.79 (-5.09, 8.78)	1.48 (-6.28, 9.45)	-0.88 (-8.93, 7.28)	<b>D</b>	-1.55 (-10.48, 7.20)	0.33 (-8.98, 9.72)	-2.02 (-13.57, 9.10)	
3.36 (-2.03, 8.82)	3.00 (-2.62, 8.99)	0.72 (-4.18, 5.58)	1.55 (-7.20, 10.48)	<b>E</b>	1.90 (-5.49, 9.47)	-0.49 (-7.63, 6.54)	
1.45 (-4.93, 7.92)	1.10 (-5.90, 8.39)	-1.22 (-7.63, 5.38)	-0.33 (-9.72, 8.98)	-1.90 (-9.47, 5.49)	<b>F</b>	-2.45 (-12.73, 7.89)	
3.92 (-4.97, 12.88)	3.54 (-5.27, 12.90)	1.23 (-7.37, 9.90)	2.02 (-9.10, 13.57)	0.49 (-6.54, 7.63)	2.45 (-7.89, 12.73)	<b>G</b>	

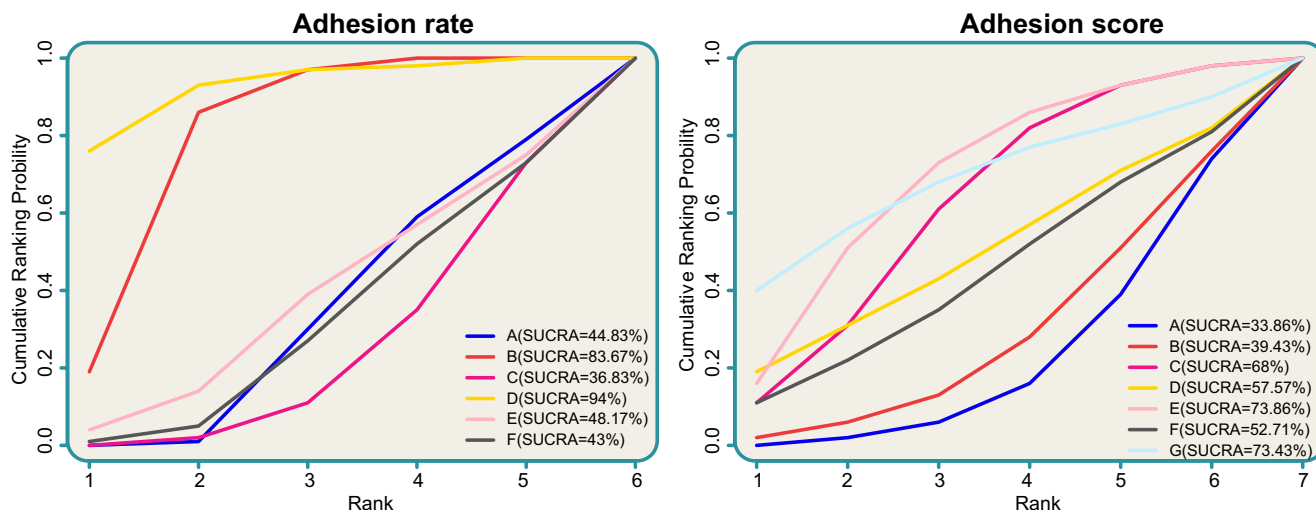
The use of bold indicates significant difference. Odds ratios/weighted mean difference and 95% confidence intervals below the treatments should be read from row to column while above the treatments should be read from column to row.

95% CI = 95% confidence interval; A = control; B = anti-blocking agent; C = intrauterine contraceptive device; D = estrogens; E = intrauterine balloon; F = Foley catheter; G = amnion graft; NA, not available; OR, odds ratio; WMD, weighted mean difference.

with IUAs, but needed to be combined with other ancillary treatments to achieve maximal outcomes.<sup>37</sup> A blinded, randomized study evaluated the fibrinolytic effects of tissue plasminogen activator, urokinase plasminogen activator, and streptokinase, and reported that both tissue plasminogen activator and urokinase plasminogen activator may be used to prevent adhesion formation during local delivery.<sup>38</sup>

Additionally, our findings demonstrated that anti-blocking agents and estrogens had relatively lower ratios of postoperative IUAs compared with the control, indicating that

anti-blocking agents and estrogens seem to be more effective in the prevention of postoperative IUAs. Similarly, a previous study investigated the association between different doses of estrogen before transcervical resection of adhesions surgery and clinical outcomes in serious IUAs, and confirmed that estradiol valerates serve as a viable alternative drug for the prevention of IUAs before and after hysteroscopic surgery.<sup>39</sup> Furthermore, a retrospective cohort study compared the efficacy of intrauterine balloon, IUDs, and hyaluronic acid gel in the prevention of the adhesion reformation after



**Figure 4** The results of surface under the cumulative ranking curve (SUCRA) of efficacy of different interventions in the prevention of postoperative intrauterine adhesions (A = control; B = anti-blocking agent; C = intrauterine contraceptive device; D = estrogens; E = intrauterine balloon; F = Foley catheter; and G = amnion graft).

hysteroscopic adhesiolysis for Asherman syndrome, and reported that insertion of an intrauterine balloon or IUD was more effective than the use of hyaluronic acid gel in the prevention of IUA reformation.<sup>4</sup> A specially designed intrauterine balloon has been manufactured by Cook Medical (UK) that fits in the uterine cavity better than the rounded balloon of the Foley catheter. In accordance with the recurring theme, we found that estrogens and intrauterine balloons achieved the highest SUCRA values, but, in general, the preventive effect of estrogens was relatively better. However, a previous study indicated that hysteroscopic adhesiolysis is the preferred choice of treatment for IUAs.<sup>40</sup> Meanwhile, another study supported the use of estrogens as perioperative adjuvant therapy for preventing recurrent adhesions, which further adds to the confusion of which is the actual optimal choice.<sup>41</sup> For network meta-analysis, the differences among direct comparison, indirect comparison, cumulative ranking probability calculation, and clustering analysis results are attributed to the effect scale index and other reasons. These differences are not contradictory trends, but the magnitude of significant results. In other words, we need to combine direct and indirect evidence and consider the outcome indicators comprehensively before we can make the research results clear step by step and finally draw reliable conclusions. In this study, we first used the node segmentation method to test the inconsistency of the two outcome indicators, and found that the results of direct and indirect evidence of all outcome indicators were consistent. Second, the main results of network meta-analysis are further clarified on the basis of pairwise meta-analysis results. By calculating the cumulative ranking probability and clustering analysis, the best intervention measures were determined to be estrogens, followed by intrauterine balloons.

It is also noteworthy that 10 RCTs and two cohort studies were included in the current meta-analysis. Although RCTs are rarely carried out in the field of surgery, the results are still clinically significant, and well-designed non-RCTs with high-quality were also included. Moreover, the statistical analysis was conducted in correct ways. In this meta-analysis, the

patients were treated with hysteroscopic, adhesiolysis, and transection, respectively. There are differences in these basic conditions. However, due to limited existing literature, we could only explore the difference in the preventive effects of different interventions (anti-blocking agents, IUDs, estrogens, intrauterine balloons, Foley catheters, and amnion grafts) on IUAs after a certain operation. Therefore, strict inclusion and exclusion criteria were set, and further restrictions were placed on age, outcome indicators, document quality, and sample size. It is notable that all data of the outcome indicators of IUAs were obtained from the results of hysteroscopy after 1–2 months. For adhesion scores, we take the difference before and after intervention for meta-analysis, which to some extent, eliminates the baseline data differences and greatly reduces heterogeneity. In addition, the results of direct evidence and indirect evidence of all outcome indicators were consistent, making our findings much more concrete. Nevertheless, there were some limitations in the current study. First, variations in treatment duration or dose of the same intervention could have possibly contributed to variations in study outcomes. However, different treatment duration of the same intervention was not feasible owing to insufficient patients and events to form a well-connected network, so we solely evaluated treatment effects of major intervention classes. Second, the sample size of the six interventions and the number of direct comparisons between interventions were different, which also might have influenced the results. Third, because the recurrence of IUAs could reach as high as 60%, the prevention of IUAs may be divided into two parts, primary and secondary ones. However, the present study failed to make a distinction between them, which need further clarification. Last, the application of strict inclusion and exclusion criteria could not cover the presence of differences in basic conditions and possibility of adhesion formation following the different surgical procedures, which might influence the presented result. Because the purpose of this meta-analysis is to compare the efficacy of different interventions in the prevention of postoperative IUAs, the outcome

index is limited to the situation of IUAs, but the different bias risks of different surgical effects and prognosis need another study to elucidate.

In conclusion, our findings demonstrated that estrogens are the relatively better intervention for the prevention of postoperative IUAs. This network meta-analysis represents the most comprehensive synthesis of data for currently available pharmacological treatments for patients with IUAs. All included studies were presented with NOS assessment, and, therefore, the results of our network meta-analysis are credible and reliable. In addition, our updated synthesis of existing data provides a new insight for the prevention of postoperative IUAs. However, there is a need for further studies with the development of these interventions.

**Supporting Information.** Supplementary information accompanies this paper on the *Clinical and Translational Science* website ([www.cts-journal.com](http://www.cts-journal.com)).

**Figure S1.** Flowchart showing literature search and study selection.

**Figure S2.** Quality assessment of the 12 enrolled studies according to NOS score (NOS: Newcastle-Ottawa Scale).

**Figure S3.** Cluster analyses for different efficacy of different interventions in the prevention of postoperative intrauterine adhesions (A = control; B = anti-blocking agent; C = intrauterine contraceptive device, IUD; D = estrogens; E = intrauterine balloon; F = Foley catheter).

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