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Review Article

Short- and Long-term Outcomes of Postoperative Intrauterine Application of Hyaluronic Acid Gel: A Meta-analysis of Randomized Controlled Trials

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ABSTRACT **Objective:** To systematically evaluate the role of hyaluronic acid (HA) gel and its derivatives in the postoperative prevention of intrauterine adhesions (IUA) and to assess whether HA gel could improve the pregnancy rate.

Data Sources: A structured search was performed in PubMed, Cochrane, Scopus, Web of Science, and Embase on February 2, 2022.

Methods of Study Selection: We chose medical subject headings and relevant terms from other articles for the database search. The following intervention was selected: HA gel or related derivatives vs placebo in randomized controlled trials (RCTs). The following outcomes were selected: the rate and severity of IUA after intrauterine operations and pregnancy rate. After the full-text screening, 12 articles were included in the final analysis. The study quality and risk of bias were assessed with the Cochrane tool (www.training.cochrane.org/handbook).

Tabulation, Integration, and Results: Data from 12 articles on 1579 patients were extracted and analyzed by 2 independent reviewers. According to the meta-analysis, HA gel could decrease the risk of IUA (risk ratio [RR], 0.50; 95% confidence interval [CI], 0.37−0.67; p = .005; I^2 = 59%) after intrauterine operations. Subgroup analysis revealed a significant positive impact of HA gel on both groups receiving dilatation and curettage (RR, 0.42; 95% CI, 0.30−0.59; p = .86; I^2 = 0) or hysteroscopic surgery (RR, 0.55; 95% CI, 0.38−0.80; p = .007; I^2 = 66%). The sensitivity analysis showed that heterogeneity could be improved significantly by removing one study. The severity of IUA (mean difference = −0.92; 95% CI, −1.49 to −0.34; p <.00; I^2 = 89%) was lower in the intervention group. Subgroup and sensitivity analyses did not significantly improve the heterogeneity. When the studies are classified by the volume of HA gel, 10 mL (RR, 0.40; 95% CI, 0.27 −0.60; p = .96; I^2 = 0) and 5 mL (RR, 0.34; 95% CI, 0.14−0.82; p = .36; I^2 = 0) were effective in treating IUA. In contrast, HA gel <5 mL was not sufficient to prevent IUA (RR, 0.66; 95% CI, 0.43−1.01; p = .02; I^2 = 71%; p = .05). The pregnancy rate was also improved by the use of HA gel (RR, 1.39; 95% CI, 1.13−1.72; p = .37, I^2 = 0).

Conclusion: HA gel helps prevent IUA and decreases the severity of IUA after intrauterine surgery. A greater volume (≥5 mL) of HA gel is recommended to prevent IUA, according to this analysis. Moreover, HA gel can increase the pregnancy rate after intrauterine surgery. However, these conclusions should be interpreted with caution because of the inadequate quality of some RCTs with relatively small sample sizes and sample heterogeneity. Large RCTs are required to verify these conclusions in the future. Journal of Minimally Invasive Gynecology (2022) 29, 934−942. © 2022 AAGL. All rights reserved.

Keywords: Intrauterine adhesion; Hyaluronic acid gel; Meta-analysis

Yuya Dou and Tingting Yu contributed equally to this paper and should be considered as the co-first authors.

The authors declare that they have no conflict of interest.

Data sharing not applicable. All data in this paper were public.

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Fritsch [1] was the first to describe amenorrhea due to intrauterine adhesions (IUA) caused by dilatation and curettage (D&C) in 1894. Asherman [2,3] described the Asherman syndrome in a series of papers published in 1950. Since then, many articles have been published, and much attention has been paid to this condition. However, the etiology, underlying mechanisms, and management strategy of IUA are still not clearly understood [4]. Iatrogenic trauma to the uterus is the main cause of IUA, including cesarean delivery, D&C for abortion and retained products of conception, and hysteroscopic surgery [5]. Infection, placenta accreta, and other intrauterine changes that impair endometrial healing also cause IUA [6]. Other factors such as race, age, geographic location, and lifestyle may also play a role in intrauterine fibrosis [7]. Several postoperative treatments have been proposed as anti-adhesive methods. One of the most widely accepted anti-adhesive agents is hyaluronic acid (HA) gel. HA gel is a semisolid substance that serves as a physical barrier and a biological agent to prevent adhesions. However, early randomized controlled trials (RCTs) on the efficacy of HA for IUA prevention provided contradictory results [8−10]. Because additional RCTs on this topic have been conducted recently, we aimed to search the databases and perform a meta-analysis to draw conclusions on the efficacy of HA gel for IUA after intrauterine operations.

Methods

Literature Screening

This meta-analysis was performed based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines [11] and was registered in the International Prospective Register of Systematic Reviews (ID: CRD42022312678). We systematically searched the related articles in the electronical databases including PubMed, Cochrane, Scopus, Web of Science, and Embase by using the following relevant terms and medical subject headings: "Hyaluronic Acid (MeSH)" OR "hyaluronic acid gel (All fields)" OR "auto-crosslinked hyaluronan gel (All fields)" OR "hyalobarrier (All fields)," "hyalobarrier gel (All fields)" OR "hyaluronan gel (All fields)" OR "auto-crosslinked hyaluronic acid gel (All fields)" OR "auto-crosslinked hyaluronan gel (All fields)" OR "autocrosslinked hyaluronan gel (All fields)" OR "auto crosslinked hyaluronan gel (All fields)" OR "ACP gel (All fields)" OR "auto-crosslinked polysaccharide polymer gel (All fields)" AND "Gynatresia (MeSH)" OR "intrauterine adhesions (All fields)" OR "IUA (All fields)" OR "endometrial injury (All fields)" OR "intrauterine adhesion (All fields)" OR "postoperative adhesion (All fields)" OR "Fritsch syndrome (All fields)" OR "synechia uteri (All fields)" OR "IUAs (All fields)" OR "uterine adhesion (All fields)" OR "uterine atresia (All fields)" OR "uterine atrophy (All fields)" OR "cervical atresia (All fields)" OR "sclerotic endometrium (All fields)" OR "endometrial sclerosis (All fields)" OR "traumatic amenorrhea (All fields)" OR "adhesive endometriosis (All fields)" OR "post-traumatic intrauterine synechiae (All fields)" AND "randomized controlled trial (Publication Type)" OR "randomized (Title/Abstract)" OR "placebo(Title/Abstract)." Language, geological, and race restrictions were not used. Most non-English publications had English abstracts; we also used Google and sought help from translators to translate the crucial parts of these non-English articles.

Study Selection

Study inclusion criteria were as follows: (1) study design: RCTs that compared the short-and long-term outcomes of patients who received HA gel or related derivatives vs placebo after intrauterine operations; (2) outcomes: the rate and severity of IUA and pregnancy rate.

The study exclusion criteria were as follows: (1) non-RCTs, including case reports, reviews, conference abstracts without adequate information, quasi-RCTs, observational and retrospective studies; (2) studies with animal experimentation; and (3) studies in which abdominal surgery was performed at the same time.

Data Extraction and Quality Assessment

Literature screening, data extraction, and quality assessment were independently performed by 2 reviewers (Y.D. and T.Y.). IUA were graded with the 1988 American Fertility Society (AFS) scoring system [12]. The pregnancy rate was determined by the number of pregnancies/total cases. We also analyzed by HA gel volume and by stratifying according to the intrauterine procedure performed. Bias was evaluated in accordance with Cochrane Collaboration's risk of bias tool. If any disagreements occurred, the third reviewer discussed the problems until a consensus was reached. The first author's name, primary disorders, intrauterine operations, postoperative intervention, number of patients, the volume of HA gel, follow-up time, IUA data, and pregnancy rate were recorded.

Statistical Analysis

Dichotomous outcomes were expressed as risk ratios (RRs) with 95% confidence intervals (CIs). Continuous variables were represented by the mean difference and 95% CI. The chi-squared test and I^2 were used to evaluate heterogeneity. When the p value was <.1, heterogeneity was considered significant. I^2 was used to measure heterogeneity quantitatively. An I^2 <25% was considered insignificant heterogeneity, while an I^2 >50% indicated that the heterogeneity might be substantial. An I^2 >75% indicated a high

degree of heterogeneity. We chose the fixed-effect model when I^2 <50% and the random-effect model when I^2 >50%. Subgroup and sensitivity analyses were performed when considerable heterogeneity was observed. A value of p <.05 was considered statistically significant for the model. The calculation was performed using RevMan 5.4.1 software (The Cochrane Collaboration, 2020).

Results

Study Selection

The study flowchart for the procedures of this review, including literature screening, data extraction, and quality assessment, is shown in Fig. 1. Irrelevant papers were removed for several reasons. Finally, we selected 12 articles after a full-text assessment [8,9,13–22]. The studies of Angelo Hooker were serial reports based on the same RCT; the pregnancy rate was published in 2018 [23], while the result of IUA after D&C was published in 2017 [8]. Therefore, we calculated the related outcomes in our paper and considered these 2 papers as one article. One paper in Chinese was also included in this analysis.

Study Characteristics and Quality Assessment

A total of 699 studies were initially screened, and 12 RCTs were included in the final analysis. The baseline characteristics of the studies are listed in Table 1. Three studies reported results of blind D&C for retained products of conception [14,17,18]. Hysteroscopic adhesiolysis, hysteroscopic septal resection, hysteroscopic myomectomy, and hysteroscopic polyp resection were performed to treat IUA, uterine septum, submucosal myomas, and polyps, respectively. The risk of bias is shown in Fig. 2. Seven articles

Fig. 1

Study selection flow chart. IUA = intrauterine adhesions; RCT = randomized controlled trial. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. For more information, visit: http://www.prisma-statement.org/.

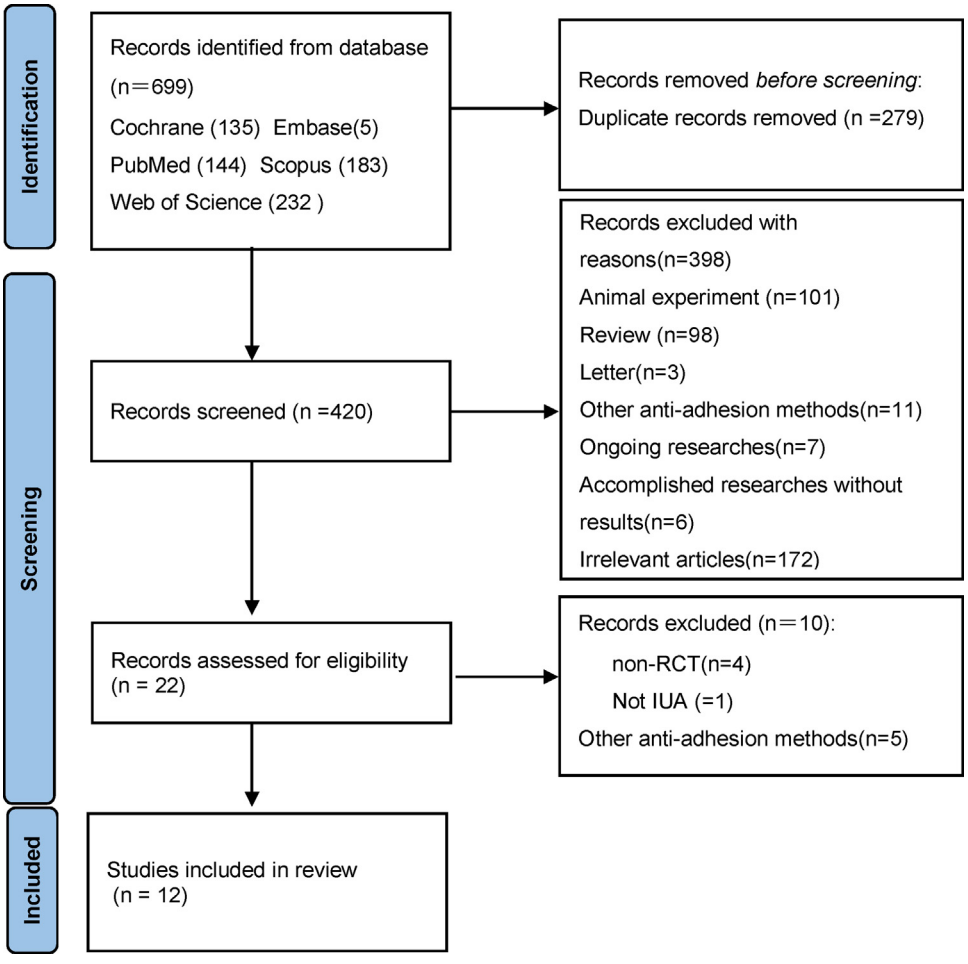


Table 1

Characteristic of the studies in this meta-analysis

Study, year	n	Disorders	Surgery	HA	Volume	Follow-up
Hookeret al, 2017 [8]	144	Miscarriage	D&C	HA gel	10 mL	12 mo
Huang et al, 2020 [16]	70	Submucosal myomas	Hysteroscopic myomectomy	Crosslinked HA gel	10 mL	12 wk
Acunzo et al, 2003 [13]	84	IUA	Hysteroscopic adhesiolysis	Auto-cross-linked HA gel	10 mL	3 mo
Vatanatara et al, 2021 [20]	62	First-trimester abortion	Vacuum aspiration	Alginate carboxymethylcellulose HA gel	5 mL	8−12 wk
Guida et al, 2004 [15]	132	Intrauterine disease*	Hysteroscopy	Auto-crosslinked HA gel	10 mL	3 mo
Zhou et al, 2021 [22]	245	IUA	Hysteroscopic adhesiolysis	Auto-crosslinked HA gel	3 mL	4 wk
Tafti et al, 2021 [19]	65	Uterine septal	Hysteroscopic septal resection	HA gel	1 mL	2 mo
Sroussi et al, 2019 [18]	278	Miscarriage	D& C	HA gel		6−8 wk
Can et al, 2018 [14]	48	Miscarriage	D& C	Crosslinked hyaluronan gel	5 mL	2−6 mo
Xiao et al, 2015 [21]	111	IUA	Hysteroscopic adhesiolysis	Auto-crosslinked HA gel	2 mL	3 mo
Xiaoyan Mao 2019 [9]	61	IUA	Hysteroscopic adhesiolysis	Crosslinked hyaluronan gel		1 mo
Xue Ying Li 2018 [17]	274	Miscarriage	D&C	Crosslinked hyaluronan gel	3 mL	3 mo

D&C = dilatation and curettage; HA = hyaluronic acid; IUA = intrauterine adhesions.
* Including submucous myomas or endometrial polyps or uterine septa.

provided clear methods for generating randomization sequences [8,9,13,15,16,19,22]. Six studies provided actual allocation concealment procedures [8,9,13,15,16,22]. Eight articles did not report the actual procedures of blinding [9,14,18,19,21]. One article did not mention the necessity of blinding [20]. All the articles reported the rate of IUA.

Meta-analysis Results

The rate of IUA after intrauterine operation was lower in patients who received HA gel (RR, 0.50; 95% CI, 0.37 −0.67; p = .005; I^2 = 59%) (Fig. 3). Because of the significant heterogeneity in the studies, we performed a sensitivity analysis. When we excluded the study by Mao et al [9], the heterogeneity of the analysis was improved (RR, 0.49; 95% CI, 0.40−0.59; p = .34; I^2 = 11%), and the outcomes of the analysis were still established (Fig. 4). Subgroup analysis confirmed the protective role of HA gel in patients after D&C (RR, 0.42; 95% CI, 0.30−0.59; p = .86, I^2 = 0) or hysteroscopic surgery (RR, 0.55; 95% CI, 0.38−0.80; p = .007; I^2 = 66%) (Fig. 5). When we removed the study by Mao et al [9], the heterogeneity in the group with hysteroscopic surgery also improved (RR, 0.54; 95% CI, 0.43−0.69; p = .15; I^2 = 38%). Only 7 articles reported the AFS scores [8,9,13,15,17,21,22]. The meta-analysis of these 7 articles showed that HA gel had a significant effect on IUA severity (mean difference = −0.92; 95% CI −1.49 to −0.34; p <.00; I^2 = 89%) (Fig. 6). Subgroup and sensitivity analyses did not significantly change the heterogeneity of the studies. Ten studies reported the volume of HA gel. These studies used only 1 dose of HA gel after the intrauterine operations in the intervention group. Subgroup analysis of the volume of HA gel showed that 10 mL (RR, 0.40; 95% CI, 0.27 −0.60; p = .96; I^2 = 0) and 5 mL (RR, 0.34 95% CI, 0.14 −0.82; p = .36; I^2 = 0) were effective in IUA prevention. However, treatment effectiveness in the group with <5 mL

Fig. 2

The risk of bias assessment.

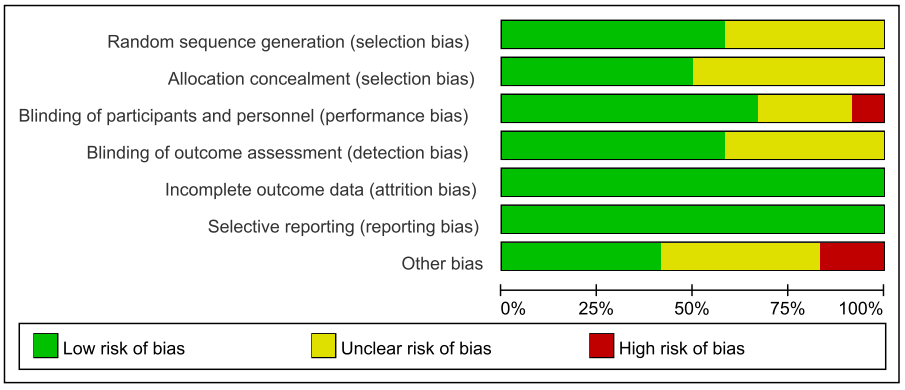
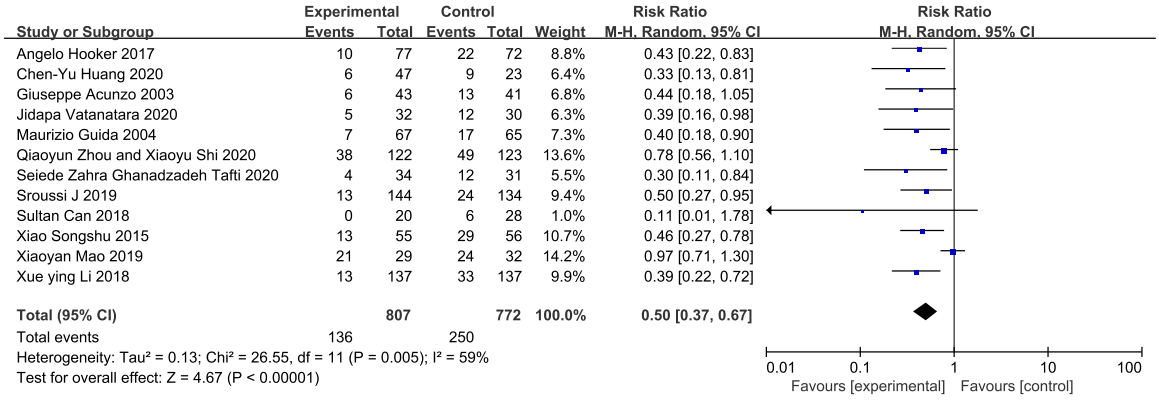


Fig. 3

Forest plot of the rate of IUA after intrauterine operations. CI = confidence interval; IUA = intrauterine adhesions.



HA gel was not confirmed (p = .05) (Fig. 7). Only 3 studies reported long-term outcomes [9,18,23], in which the pregnancy rate was improved in patients with application of HA gel after intrauterine operations (RR, 1.39; 95% CI, 1.13 −1.72; p = .37; $I^2 = 0$) (Fig. 8).

Discussion

A total of 12 RCTs were included in this meta-analysis, which had more RCTs and participants than any previous reviews. Most RCTs were published in the past 5 years with acceptable quality. All of them reported the efficacy of HA gel in preventing IUA after intrauterine operations, while 7 reported the AFS score. Ten studies reported the volume of HA gel, while 3 reported the pregnancy rate. Regardless of the type of operation, the rate and severity of IUA after intrauterine operations were lower in the intervention group, which is consistent with recent analyses [24,25]. Moreover, our review indicates the importance of a sufficient volume of HA gel to prevent IUA, which has never been mentioned in other systematic reviews and meta-analyses. A few reviews discussed the long-term outcomes of HA gel because many RCTs did not report related data, and some reviews held negative views about this problem [26,27]. However, our research supports the positive role of HA gel in improving the pregnancy rate.

The precise incidence of IUA remains unclear because most cases are asymptomatic or have vague symptoms. While the prevalence of IUA after certain diseases or surgeries has been reported, the rates fluctuate greatly depending on the diagnostic methods and study populations [28−31]. Hysteroscopy is considered the gold standard for IUA evaluation [32]. Many treatments have been proposed to avoid IUA or decrease its severity. Intrauterine devices [33], amniotic membranes [34], estrogens [35], platelet-rich plasma [36], HA gel or related derivatives [37], and intrauterine balloons [38] have been used to prevent IUA. The efficacy of these treatments has not been ultimately proven because

Fig. 4

Forest plot of the rate of IUA after intrauterine operations when excluding the study by Mao et al [9]. CI = confidence interval; IUA = intrauterine adhesions.

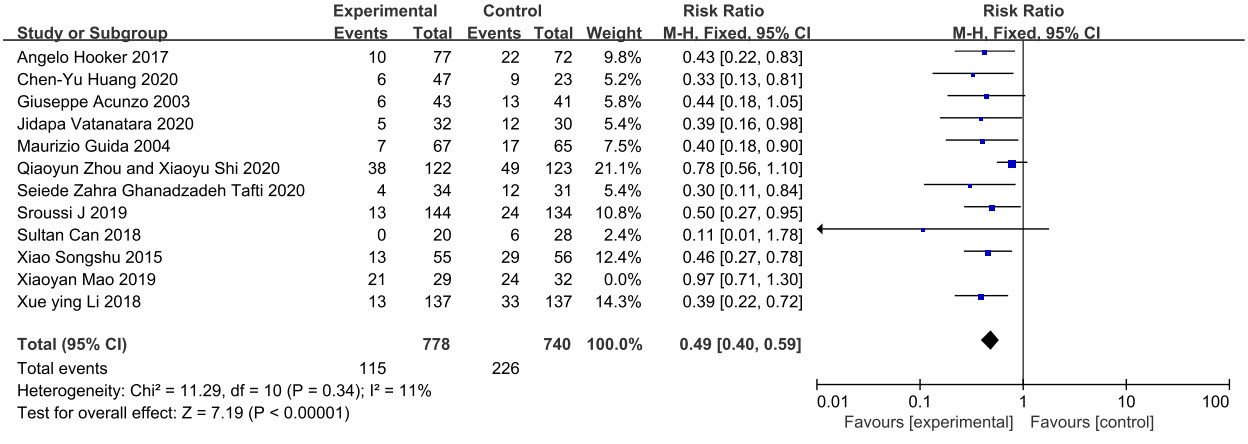


Fig. 5

Forest plot of the severity of IUA after intrauterine operations. CI = confidence interval; IUA = intrauterine adhesions.

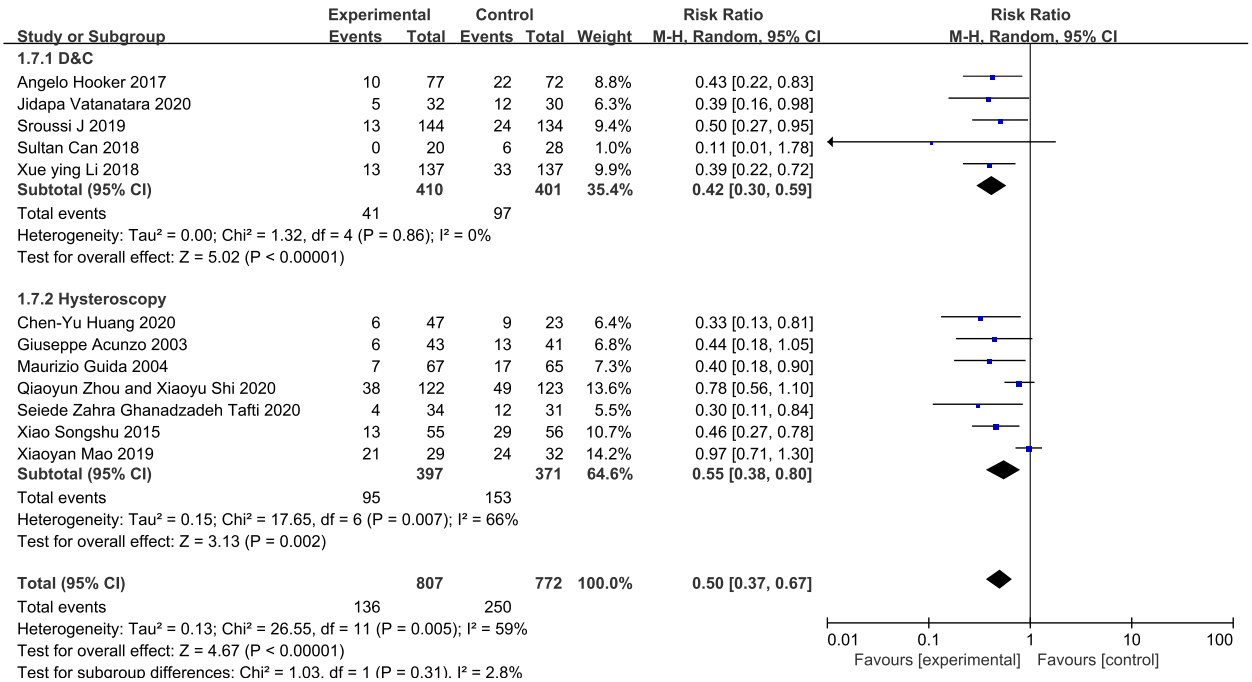
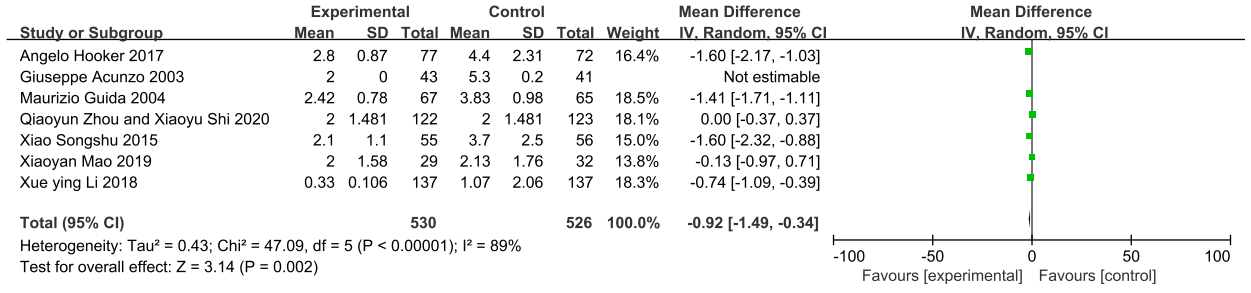


Fig. 6

Forest plot of different intrauterine operations. CI = confidence interval; SD = standard deviation.



high-quality research is lacking. HA is a disaccharide that consists of linear polysaccharides. HA gel can be used not only as a mechanical barrier to avoid the attachment of fibrin but also as an anti-adhesive agent because of its anti-inflammatory property and its ability to dissolve fibrin [39].

This meta-analysis found that HA gel decreased the occurrence of IUA after intrauterine surgery (Fig. 3). Subgroup analysis demonstrated that HA gel could decrease the rate of IUA regardless of the intrauterine operations (Fig. 5). After removing the study by Mao et al [9], the heterogeneity improved significantly (Fig. 4). This study focused on the effect of crosslinked hyaluronan gel on the pregnancy rate. Notably, second-look hysteroscopy was only performed in 14.4% (29 patients) of the treatment group [9]. Other studies have shown a much higher ratio of second-look hysteroscopy. This may account for the negative results regarding the rate of IUA after intrauterine operations and the heterogeneity in this meta-analysis. Seven articles with reported AFS scores were used to evaluate whether HA gel could lower the severity of IUA. Although the heterogeneity was significant (Fig. 6), our meta-analysis confirmed the effectiveness of HA gel for this indication. Sensitivity analysis showed that no studies that could significantly alter the heterogeneity of our meta-analysis were identified. In these studies, the criteria to evaluate IUA were relatively subjective as the items, such as menstrual patterns, in the AFS scoring system, which were employed in all studies, were not absolutely objective. Different types

Fig. 7

Forest plot of the rate of IUA after patients received different HA gel volumes. CI = confidence interval; IUA = intrauterine adhesions.

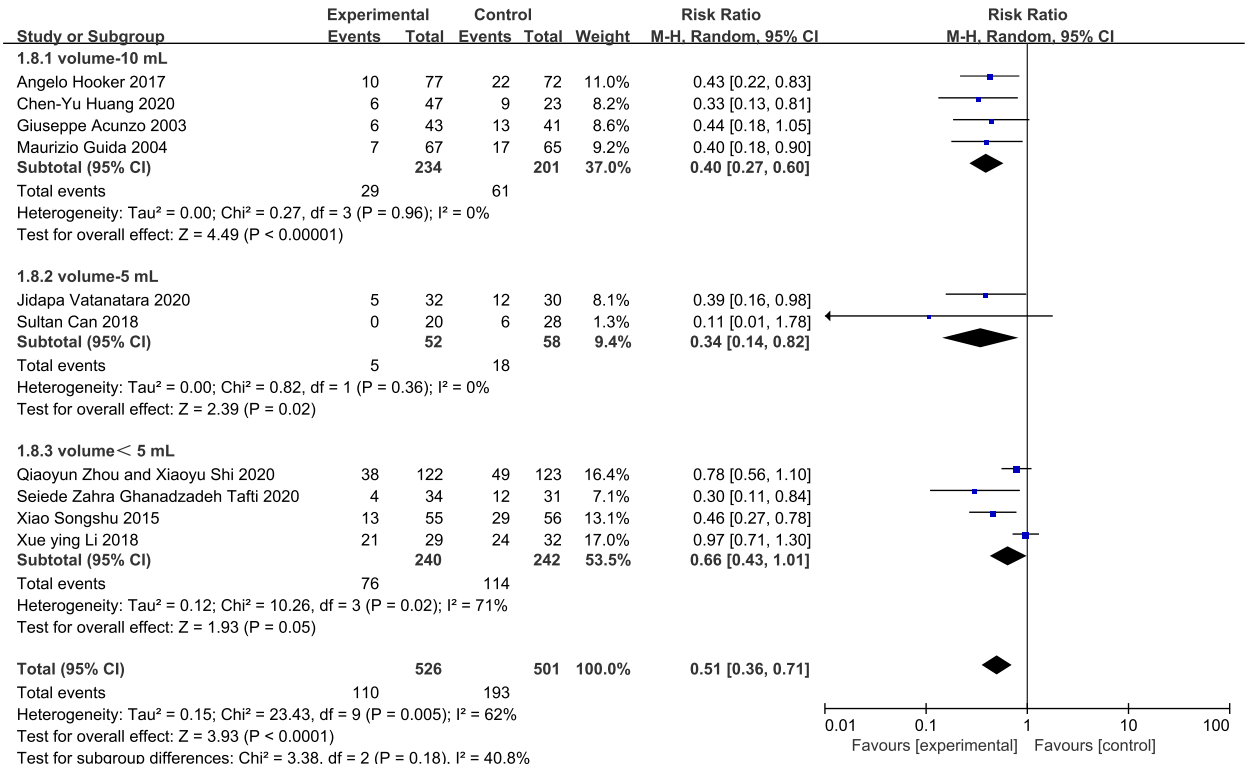
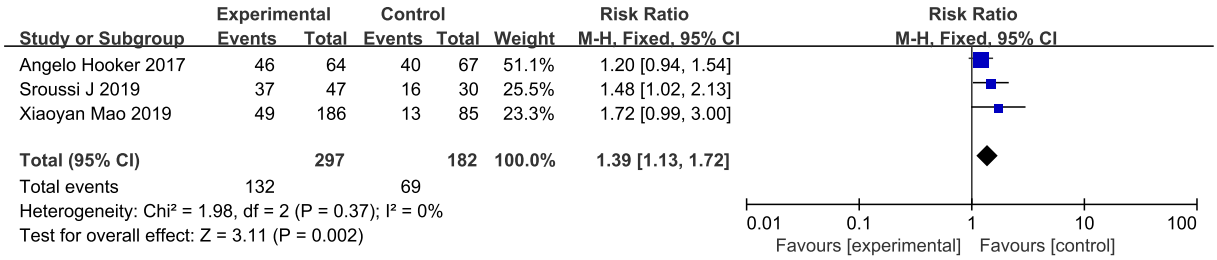


Fig. 8

Forest plot of the pregnancy rate after HA gel application. CI = confidence interval.



of disease, surgeons, and volumes of HA gel were described in these studies. These variables may also account for the heterogeneity in evaluating the severity of IUA. This result should be interpreted carefully because of this significant heterogeneity. Other studies by Fei et al [40] and Cheng et al [24] also supported the anti-adhesive role of HA. However, their sample sizes were small, and other types of carriers for HA were included in these studies.

We also analyzed the amount of HA used in the studies and found that HA showed a protective effect only when HA gel volume was ≥5 mL (Fig. 7). The unspecified concentration of HA gel may also affect the results, which were difficult to calculate because these RCTs were carried out in different countries with HA gel from different factories. However, a larger volume of gel was used in these RCTs, and more HA content was also undoubtedly introduced into the uterine cavity. Our research showed favorable short-term results in patients with the application of HA gel volume ≥5 mL. Therefore, we should actively increase the HA gel volume to prevent IUA after intrauterine operations. Because there were no similar articles analyzing whether the volume of HA gel could affect short-term outcomes, the results of our analysis should be verified

in future research. The pregnancy rate of patients who received HA gel was higher than that of those who did not (Fig. 8). However, the long-term outcomes of HA gel for patients of childbearing age have been contradictory in other studies [27,40]. These discrepancies might result from different study selection criteria, such as the primary disease of the patients and the type of research (RCT or non-RCT). For example, a meta-analysis performed by Fei et al [27] pointed out that HA gel had no significant effect on pregnancy rate. However, this result was derived from only 2 articles, which included 122 patients and were retrospective studies [10,41].

In conclusion, our meta-analysis supports the anti-adhesive role of HA gel and suggests that HA gel could improve the pregnancy rate after intrauterine surgery. We also point out the necessity of a sufficient volume of HA gel to exert an anti-adhesive function. However, the heterogeneity, relatively small sample size, low quality of some RCTs, and some confounders that could not be controlled and calculated are the major limitations of this meta-analysis. Therefore, more strictly designed RCTs are required to assess the short-and long-term outcomes of HA gel application after intrauterine operations.

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