Original Article

Comparison of Autocross-Linked Hyaluronic Acid Gel and Intrauterine Device for Preventing Intrauterine Adhesions in Infertile Patients: A Randomized Clinical Trial

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Abstract

Objectives: The objective of this study is to evaluate the efficacy of autocross-linked hyaluronic acid (HA) compared with intrauterine device (IUD) for preventing intrauterine adhesions (IUAs) in infertile patients after hysteroscopic adhesiolysis.

Materials and Methods: A randomized clinical trial (ChiCTR-IOR-16007746). Upon completion of adhesiolysis, 3 ml of HA gel was placed into the uterine cavity in Group A; 3 ml of HA gel and an IUD were placed in Group B; and only an IUD was placed in Group C. A second hysteroscopic examination was performed in all patients at approximately 1 month postoperatively for the evaluation of IUA. The primary outcome measure was the effective rate of IUA prevention based on the American Fertility Society (AFS) scoring system.

Results: Eighty-nine women were randomly distributed into two groups for intention to treat with 30 patients in Group A, 24 patients in Group B, and 35 patients in Group C. Patients were scored and stratified into three degrees and were enrolled using the simple random sampling method. The three groups were well balanced. There were no significant differences in age, endometrial thickness, the previous number of pregnancy, and the distribution of adhesion categories across mild, moderate, and severe between the three groups. The effective rate of IUA prevention, the AFS score after therapy, and the percentage improvements of Chinese score and AFS score before and after surgery were statistically significant difference between Groups A and C. The clinical pregnancy rate in Group A was higher than those in Groups B and C, but the difference was not statistically significant.

Conclusion: HA gel has an advantage over an IUD in reducing IUA recurrence and decreasing adhesions.

Keywords: Hyaluronic acid, hysteroscopy, intrauterine adhesions

Introduction

Intrauterine adhesion (IUA) is a disease caused by the injury of the endometrial basal layer. In the healing process, opposing walls of the uterus adhere together causing minimal, marginal, or complete obliteration of the uterine cavity.[1] IUA may cause a poor reproductive outcome, especially recurrent miscarriage. Over the last four decades, hysteroscopy has become the standard method used

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to diagnose and treat this condition.[2] Hysteroscopic adhesiolysis aims to restore the shape and volume of the uterine cavity to enhance the fertility potential.[3,4] A number of approaches have been proposed to reduce adhesion reformation after hysteroscopy adhesiolysis, such as hormone treatment and intrauterine barriers, including mechanical barriers and absorbable barriers.[5] Several recent studies have focused on the use of an IU balloon, IU contraceptive device, and hyaluronic acid (HA) gel,[2,6-8] human amniotic mesenchymal stromal cells, etc., as postoperative adjuvants. Many clinical trials have been conducted to compare the different adhesion preventing methods. However, till now, there is a lack of definitive evidence to conclude that any treatment is effective in preventing posthysteroscopy IUA formation.[9] In fact, an ideal adjunctive therapy following hysteroscopic adhesiolysis such as HA plays a role in inflammation, granulation, and reepithelialization for wound healing.[10-12]

HA has also been suggested as an effective method to reduce the presence and extent of IUAs.[13] HA seems particularly suitable for preventing adhesion formation because of its highly adhesive properties and more prolonged residence time on the injured surface than unmodified HA.[14] HA gel plus balloon has been shown to be better than balloon alone and could effectively decrease the adhesion severity and improve menses postoperatively.[15] However, trials that compare HA and an intrauterine device (IUD) are rare.

In 2015, a new classification system of IUA was promoted by Chinese experts [Supplementary Table 1].[16] We registered and conducted a randomized clinical trial (ChiCTR-IOR-16007746) to examine whether the intrauterine application of HA gel could be a better barrier than an IUD after operative hysteroscopy for IUA based on both this new score system and the American Fertility Society (AFS) scoring system. Our hypothesis is that the HA may be better than an IUD in preventing IUA recurrence.

Materials and Methods

This was a single-center randomized controlled trial (RCT). The protocol of this study was approved by the Institutional Review Board (IRB no. [2015] 39). First, we designed three trials, including one comparing with HA and without HA, one comparing with an IUD and without an IUD, and one comparing with HA and IUD. However, the first two trials could not receive IRB approval. If we set a blank control group without HA or IUD, patients would not be willing to participate in our research. Patients would ask doctors to place something into the uterus to prevent relapse. Therefore, we designed this trial. The sequence of simple randomization was generated through Excel and maintained by a doctor who was not involved in patient enrolment. The sequence was not accessible to any investigator. The assignments were placed into opaque envelopes and were opened before the surgery. Written informed consent was obtained before study enrollment. The study project was registered on the Chinese clinical trial registry platform.

The autocross-linked HA gel was donated by the BioRegen Biomedical (Changzhou) Company Limited, Jiangsu Province, China, and was free for patients who were enrolled in Groups A and B.

Our center is one of the three major reproductive centers in China, carrying out more than 10,000 *in vitro* fertilization (IVF) cycles every year. The center has an independent reproductive surgery ward, which can carry out reproductive surgery. The center carries out more than 1000 cases of IUA separation every year. Patients with IUA diagnosed by hysteroscopy were invited to participate in the study. The enrolment time was from December 2015 to March 2016. All the surgeries were performed before March 2016. The first follow-up stage represented the second hysteroscopy and other records. The second stage of follow-up was closed by May 2018 and focused on fertility outcomes. The day of opening the envelope was considered study day 1.

The inclusion criteria were infertile women (failure to establish a clinical pregnancy after 12 months of regular and unprotected sexual intercourse) aged 20–44 with mild-to-severe IUA diagnosed by hysteroscopy at our center. The exclusion criteria included patients with surgical contraindications, patients with contraindications for postoperative hormone replacement therapy, patients with fibroids and uterus anomalies, or patients who were allergic to HA or IUD. Each patient was informed of the operation procedure by a doctor. The surgeries of electronic hysteroscopic adhesiolysis were performed by six surgeons in our center under general anesthesia in the early follicular phase of the menstrual cycle. The six doctors were attending doctors with professional training. They all had more than 10 years of work experience.

The scores of both the AFS system and the Chinese system were calculated during the surgery. Placement of the IUD, HA, or HA plus IUD in the intrauterine cavity was performed according to the assignment envelope content during the operation. The application of HA was performed by its special catheter. We use Yuan Gong medicated Cu-IUDs, provided by Yantai Family Planning Medical Device Company Limited. The IUD contains 200 mm^2 of copper. It is made of stainless-steel wire and medical silica gel, containing an average of 25 mg of indomethacin. HA was put into the intrauterine cavity ahead of IUD in Group C.

Neither the patients nor the surgeons taking down the synechia was blinded to the treatment. In order to protect the endometrium, we do not routinely take endometrial pathology for patients with IUAs. Patients' husbands were informed about the received treatment by the operator after the envelope was open and before the surgery was over. Both the initial diagnostic hysteroscopy and the 1-month follow-up hysteroscopy (second hysteroscopy) were performed by the same six surgeons in our center, but different surgeons may have performed the two surgeries in individual patients. During the postoperative hysteroscopy review, the IUD group and the non-IUD group (HA plus IUD group and IUD group) could not be blinded. However, during hysteroscopy review, the operator was unable to distinguish the HA plus IUD group from the IUD group. The HA plus IUD group and the IUD group were blind.

Postsurgical assessors who were blinded to the randomization performed the second hysteroscopy and evaluated the adhesion score. IUDs were removed at the second hysteroscopy. Mild local new adhesions identified at the 1-month follow-up visit were removed after scoring by scissors. No severe adhesions reoccurred. Estrogen therapy was given to all the patients immediately after surgery for two menstrual cycles. The postsurgical assessor performed the second hysteroscopy. The second hysteroscopy was performed to all patients after the first menstruation postoperatively. B ultrasound was conducted on day 12–14 after the second menstruation to evaluate endometrium thickness. To make the three groups comparable, the patients in our study had similar postoperation treatment and took two cycles of estrogen treatment. When choosing treatment options, doctors made recommendations based on the patient's condition. Some patients chose natural pregnancy, but most of our patients chose IVF.

A decrease of 3 in the AFS score after therapy was defined effective. The primary outcome was the effective rate of IUA prevention, which was defined by the number of effective patients divided by the total number of patients per group. The secondary outcomes include the percentage improvement (PI) of the score, endometrial thickness (EMT), and clinical pregnancy rate. The recurrence of IUA defines as the appearance of *de novo* adhesion formation at second-look hysteroscopy. PI was defined as (score before surgery-score after surgery)/score before surgery. EMT was measured. Clinical pregnancy rate was the number of patients with a visible gestation sac in the uterine cavity divided by the number of patients who underwent the first embryo transfer cycle after surgery.

We report deviations from our primary protocol that was registered on the website (http://www.chictr.org.cn/edit.aspx?pid = 12857andhtm = 4). The inclusion criteria were different from those we registered on the website because we only included patients with IUA in this study and patients with sub-mucus fibroids and uterine septum were not included. The inclusion of only one disease made the analysis and write-up easier. We also reported the clinical pregnancy rate as one of the outcomes because the follow-up time was long enough and because we wanted to add more valuable information to our paper.

The study was designed to have a power of 80% at a two-sided significance level of 0.025 to detect an absolute difference of 40% in the effective rates between the three groups on the basis of anticipated rates of 40% after IUD versus 80% after HA from the literature and our experience.[8] The allocation ratio was 1:1:1. We calculated that an average of 30 patients should be enrolled per study group to allow for a dropout rate of 5%.

The statistical analysis was according to the intention-to-treat principle (ITT) and the perprotocol principle (PP). Statistical analysis was performed with the use of SPSS 19.0 (IBM, Armonk, NY, USA). Differences in normally distributed variables were compared by the one-way ANOVA. ANOVA was used to compare the adhesion scores before and after surgery between Groups A, B, and C. The Chi-square test was used for the testing difference in categorical variables, with Fisher's exact test used for expected frequencies <5. $P < 0.05$ was considered statistically significant.

Results

Ninety-two patients were eligible to be enrolled in our clinical trial. However, one patient experienced uterine perforation during the operation, and two patients told the surgeons they might be allergic to some metal just before surgery and refused to participate. Therefore, only 89 patients were randomly distributed into the three groups for the intention to treat analysis: patients in Group A (n = 32) were treated with hysteroscopic adhesiolysis plus the HA (3 ml); patients in Group B (n = 23) were treated with hysteroscopic adhesiolysis plus HA (3 ml) and an IUD; and patients in Group C (n = 34) were treated with hysteroscopic adhesiolysis plus an IUD. Following randomization, two patients from Group A and one patient from Group C chose to cross over to Group B due to their husband's refusal and preference [Figure 1]. Table 1 shows the baseline characteristics of the patients before therapy. The baseline characteristics among the three groups were well balanced. There were no significant difference in the EMT before therapy, namely ITT (0.8 ± 0.15 vs. 0.7 ± 0.14 vs. 0.7 ± 0.23, P = 0.263) and PP (0.7 ± 0.17 vs. 0.7 ± 0.15 vs. 0.7 ± 0.25, P = 0.488); AFS before therapy, namely ITT (4 [4–6] vs. 5 [4–6] vs. 4 [4–6], P = 0.392) and PP (5 [4–6] vs. 4 [4–6] vs. 5 [4–6], P = 0.220); number of previous pregnancies, namely ITT (2 [1-3.75] vs. 3 [1–4] vs. 2 [1–3], P = 0.581) and

PP (2 [1–3.25] vs. 3 [1–4] vs. 2 [1–3], $P = 0.256$); or Chinese Score before therapy, namely, ITT (12.3 ± 4.6 vs. 14.0 ± 4.3 vs. 12.8 ± 3.4, $P = 0.999$) and PP (12.8 ± 4.2 vs. 13.0 ± 3.4 vs. 12.8 ± 3.4, $P = 0.994$).

Table 2 showed that there were no significant differences in the mean EMT after therapy, namely ITT (0.8 ± 0.2 vs. 0.70 ± 0.2 vs. 0.7 ± 0.2, $P = 0.414$) and PP (0.8 ± 0.2 vs. 0.70 ± 0.2 vs. 0.7 ± 0.2, $P = 0.161$) or the AFS score after therapy (ITT $P = 0.014$; PP $P = 0.010$). The Chinese scores after therapy were 7.7 ± 2.45 in Group A, 8.4 ± 2.3 in Group B, and 9.4 ± 3.56 in Group C ($P = 0.065$). The PI of Chinese score of IUA before and after therapy was 36.3 ± 12.7 vs. 34 ± 19.7 vs. 25.8 ± 14.5 ($P = 0.024$, ITT) and 57.6 ± 15.2 vs. 47.6 ± 21.4 vs. 40.1 ± 23.1, ($P = 0.004$, PP). To perform a comparison between every two groups, the P value corrected by the Bonferroni method ($\alpha = 0.05/3$) was 0.0167. Table 2 lists the up to date pregnancy outcomes of the participants. Group A showed a trend toward a higher clinical pregnancy rate than Group B or Group C, but there was no statistical significance, whatever by IVF or by natural.

Table 3 shows the pairwise comparison of the main outcome measures. The PI of the Chinese score before and after treatment with HA was significantly higher than that of IUD ($P = 0.001$). The PIs of AFS before and after treatment with HA were significantly higher than those with the IUD ($P = 0.001$). The effective rate of HA was significantly higher than IUD in both ITT and PP analysis ($P = 0.009$ and 0.003).

Table 1: Characteristics of the patients before therapy

Group	HA (A)	HA + IUD (B)	IUD (C)	*P*
Number	30	24	35	
Age	31.7±5.5	31.7±4.3	33.9±5.6	0.161
Number of previous pregnancy	2 (13.25)	3 (14)	2 (13)	0.256
Chinese score before therapy	12.8±4.2	13.0±3.4	12.8±3.4	0.994
AFS before therapy	5 (46)	5 (46)	4 (46)	0.220
EMT before therapy	0.7±0.173	0.7±0.148	0.7±0.252	0.488
Grades by Chinese score before therapy				
Mild	9.4 (3/30)	4.3 (1/24)	5.9 (2/35)	0.355
Middle	73.3 (22/30)	91.7 (22/24)	85.7 (30/35)	
Severe	16.7 (5/30)	4.2 (1/24)	8.6 (3/35)	
Grades by AFS score before therapy				
Mild	50 (15/30)	50 (12/24)	62.9 (22/35)	0.182
Middle	43.3 (13/30)	50 (12/24)	37.1 (13/35)	
Severe	6.7 (2/30)	0 (0/24)	0 (0/35)	

HA: Hyaluronic acid, IUD: Intrauterine device, AFS: American Fertility Society, EMT: Endometrial thickness

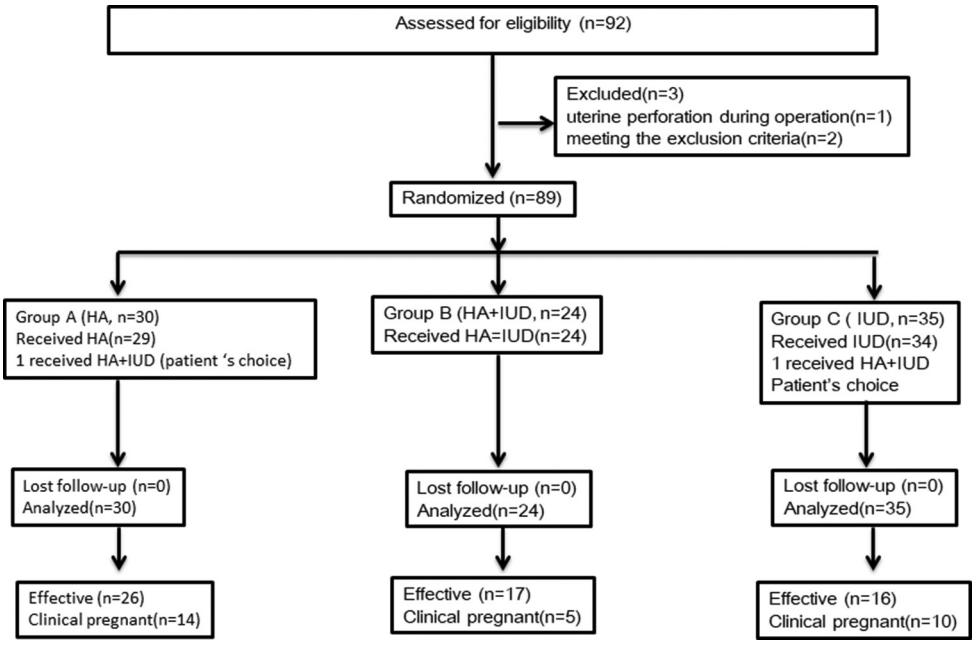

Figure 1: Study enrollment and main outcomes

Table 2: Characteristics of the patients after therapy

Group	HA (A)	HA + IUD (B)	IUD (C)	*P*
EMT after therapy	0.8±0.2	0.70±0.2	0.7±0.2	0.161
Chinese score after therapy	7.7±2.5	8.4±2.3	9.4±3.6	0.065
PI of Chinese score (%)	57.6±15.2	47.6±21.4	40.1±23.1	0.004
AFS score after therapy	0 (0)	0 (0)	3 (3)	0.014
PI of AFS (%)	100 (100100)	100 (50100)	62.5 (25100)	0.005
Clinical pregnancy rate per embryo transfer cycle (%)	61.9 (13/21)	41.7 (5/12)	42.8 (9/21)	0.377
Natural conception	1/30	0/24	1/35	0.680
Effective rate of IUA prevention (%)	86.7 (26/30)	70.8 (17/24)	45.7 (16/35)	0.002*

**P*<0.05, significant. HA: Hyaluronic acid, IUD: Intrauterine device, AFS: American Fertility Society, EMT: Endometrial thickness, IUA: Intrauterine adhesion, PI: Percentage improvement

Table 3: Group pairwise comparison of main outcome measures

Group	IUD versus HA	IUD versus HA + IUD	HA versus HA + IUD
	P	*P*	*P*
PI of Chinese score	0.001*	0.163	0.076
AFS after therapy	0.006*	0.064	0.430
PI of AFS score	0.001*	0.040	0.362
Effective rate	0.001*	0.056	0.151

**P*<0.0167, significant. HA: Hyaluronic acid, IUD: Intrauterine device, AFS: American Fertility Society, PI: Percentage improvement

Adverse events

There was one perforation before randomization. None of the 89 patients showed excessive bleeding, infection, or other complications.

Discussion

Our study revealed a reduced incidence of intrauterine readhesions in the HA groups compared to the use of IUD alone. A trend toward improved pregnancy rate was observed as well, but these results were not statistically significant. The combination of the HA gel and IUD did not offer any benefit over the HA gel only.

Recently, some studies promoted that IUD may prevent intrauterine readhesion.[17] On an account of IUD could help the physiological endometrial regeneration through keeping opposing surfaces of the uterine cavity separated, what's more removal of the IUD may also conduce to remove some adhesions which may have reformed.[18,19] In contrast, other studies report that the IUDs may have a too rather small surface area to preventing adhesion reformation.[20] Copper-bearing IUDs may induce an excessive inflammatory reaction and are not recommended for the use by the European Society of Gynecological Endoscopy.[21] Some investigators reported that the IUD may provoke local inflammation and increase the likelihood of reformation of adhesions.[19]

In our research for mild-to-severe IUA, IUD placement did not show better efficacy than HA. The endometrium after therapy and the clinical pregnancy rate had a superior trend toward in the HA group than the IUD group. In our opinion, IUDs may induce an excessive inflammatory reaction that would cause IUA recurrence and thin the endometrium. Physical barriers such as HA gel are interposed between adjacent injured surfaces to avoid direct contact after surgery.[22]

HA used in our study is a novel bio-reabsorbable membrane formulated form chemically modified HA gel and carboxymethyl cellulose. It has been proposed as an effective adjuvant to reducing the incidence of abdominal and pelvic postsurgical adhesions.[14] Animal data suggest that HA gel remains *in situ* for more than 5 ± 6 days.[19] This absorbable gel is proposed as a barrier for preventing IUA after intrauterine procedures.[14] Some studies demonstrate that the application of gel after intrauterine surgery reduces the incidence and severity of IUAs and potentially facilitates the function of the endometrium.[23,24]

Our study showed that HA could be able to reduce IUA, decrease adhesion severity, and is superior than IUD or HA plus IUD. HA gel may be an ideal barrier for preventing IUA after intrauterine procedures. A study reported that these three methods are of similar efficacy in the prevention of adhesion reformation after hysteroscopic adhesiolysis for moderate-to-severe IUAs.[25] Another study reported that for moderate-to-severe IUAs, HA gel combined with IUD may be an alternative approach for reducing adhesion recurrence after hysteroscopic adhesiolysis.[21] However, another study showed that the insertion of IUD is more effective than the use of HA in the prevention of IUA.[7] Our study demonstrated that HA was superior to IUD. The fact that the HA + IUD group had a similar adhesion rate to the IUD only group suggests the possibility that the IUD may actually be harmful.

Our research used not only the AFS but also use the new Chinese grading score of IUA. It is a new scoring system proposed by Chinese experts. Compared with other IUA

classification systems, the Chinese criteria fully consider the previous history of pregnancy and the history of curettage and firstly bring EMT into evaluation standards. Hence, even if there was no adhesion in the uterine cavity after the 2nd hysteroscopy, the score after therapy still existed because of the previous history of pregnancy and the history of curettage. It contributes to the preoperative assessment of fertility and instruction of postoperative reproduction. It will encourage the clinicians to learn about a history operation of uterine cavity operation and the EMT which will help conduct the operation and avoid the dispute caused by the postoperative thin endometrium.

In our study, Group A showed a trend toward a higher clinical pregnancy rate than Group B and Group C, but there was no statistical difference. The distribution of pregnancy after natural or IVF was similar in the three groups. According to a metaanalysis, HA gel could reduce the recurrence rate of IUAs but had no significant effect on the postoperative pregnancy rate.[26] The pregnancy rate can be affected by multiple factors. The influencing factors included the degree of uterine adhesion, times of TCRA, residual endometrial area, protocols of ovarian stimulation, and quality of embryos, etc., We do not think that the pregnancy rate can be an accurate indicator.

However, our study may have some limitations. Our sample size is too small to demonstrate the benefit of the autocross-linked HA gel over IUD for the following pregnancy outcomes. For women who want to become pregnant, reproductive outcome in general and live birth in particular is what really matters in our future study; we would like to include more patients and compare the obstetric outcomes. The allocation was not well balanced among the three groups We used the intention-to-treat analysis. Three patients changed groups after randomization. Our study is a single-center trial with relatively short follow-up time. Another limitation is that our study design lacks a placebo control. We do not know if either intervention is superior to placebo. It would be difficult for us to obtain IRB approval if we gave patients placebo treatment or left them untreated. The surgeries were performed by different surgeons, and this became one confounder in our study. However, our surgeons were well trained and had similar levels of experience. The HA was donated by the BioRegen Biomedical (Changzhou) Company Limited and was free for patients who were enrolled in Groups A and B. This may result in a deviation of the outcome.

Conclusion

The autocross-linked HA gel had an advantage over IUD in reducing IUA and decreasing adhesion severity and is proposed as a good barrier for preventing IUA after intrauterine procedures. Existing research also suggests a potential benefit for pregnancy rates. More well-designed pragmatic RCTs are needed to assess whether the use of the HA is better than the use of a placebo or an IUD to prevent IUA regarding live birth, pregnancy, the pregnancy, and miscarriage rates in a target population of infertile women.

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Conflicts of interest

There are no conflicts of interest.

References

1. Hooker AB, Lemmers M, Thurkow AL, Heymans MW, Opmeer BC, Brölmann HA, *et al*. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: Prevalence, risk factors and long-term reproductive outcome. Hum Reprod Update 2014;20:262-78.
2. March CM. Management of Asherman's syndrome. Reprod Biomed Online 2011;23:63-76.
3. Wang J, Ju B, Pan C, Gu Y, Zhang Y, Sun L, *et al*. Application of bone marrow-derived mesenchymal stem cells in the treatment of intrauterine adhesions in rats. Cell Physiol Biochem 2016;39:1553-60.
4. Choudhary P, Singh V. Hysteroscopic intrauterine adhesiolysis resulting in positive reproductive outcome. Gynecol Minim Invasive Ther 2019;8:192-3.
5. Yu D, Wong YM, Cheong Y, Xia E, Li TC. Asherman syndrome – One century later. Fertil Steril 2008;89:759-79.
6. Myers EM, Hurst BS. Comprehensive management of severe Asherman syndrome and amenorrhea. Fertil Steril 2012;97:160-4.
7. Lin X, Wei M, Li TC, Huang Q, Huang D, Zhou F, *et al*. A comparison of intrauterine balloon, intrauterine contraceptive device and hyaluronic acid gel in the prevention of adhesion reformation following hysteroscopic surgery for Asherman syndrome: A cohort study. Eur J Obstet Gynecol Reprod Biol 2013;170:512-6.
8. Peng X, Li T, Zhao Y, Guo Y, Xia E. Safety and efficacy of amnion graft in preventing reformation of intrauterine adhesions. J Minim Invasive Gynecol 2017;24:1204-10.
9. Healy MW, Schexnayder B, Connell MT, Terry N, DeCherney AH, Csokmay JM, *et al*. Intrauterine adhesion prevention after hysteroscopy: A systematic review and meta-analysis. Am J Obstet Gynecol 2016;215:267-75.e7.
10. Saari H, Konttinen YT, Friman C, Sorsa T. Differential effects of reactive oxygen species on native synovial fluid and purified human umbilical cord hyaluronate. Inflammation 1993;17:403-15.
11. Chen WY, Abatangelo G. Functions of hyaluronan in wound repair. Wound Repair Regen 1999;7:79-89.
12. Kim T, Ahn KH, Choi DS, Hwang KJ, Lee BI, Jung MH, *et al*. A randomized, multi-center, clinical trial to assess the efficacy and safety of alginate carboxymethylcellulose hyaluronic acid compared to carboxymethylcellulose hyaluronic acid to prevent postoperative intrauterine adhesion. J Minim Invasive Gynecol 2012;19:731-6.
13. Tsapanos VS, Stathopoulou LP, Papathanassopoulou VS, Tzingounis VA. The role of Seprafilm bioresorbable membrane in the prevention and therapy of endometrial synechiae. J Biomed Mater Res 2002;63:10-4.
14. De Iaco PA, Muzzupapa G, Bigon E, Pressato D, Donà M, Pavesio A, *et al*. Efficacy of a hyaluronan derivative gel in postsurgical adhesion prevention in the presence of inadequate hemostasis. Surgery 2001;130:60-4.

15. Xiao S, Wan Y, Zou F, Ye M, Deng H, Ma J, *et al*. Prevention of intrauterine adhesion with auto-crosslinked hyaluronic acid gel: A prospective, randomized, controlled clinical study. Zhonghua Fu Chan Ke Za Zhi 2015;50:32-6.
16. Chinese Society of Obstetrics and Gyneocology, Chinese Medical Association. Expert consensus on the diagnosis and management of intrauterine adhesions in China. Zhonghua Fu Chan Ke Za Zhi 2015;50:881-7.
17. Chen FP, Soong YK, Hui YL. Successful treatment of severe uterine synechiae with transcervical resectoscopy combined with laminaria tent. Hum Reprod 1997;12:943-7.
18. Ventolini G, Zhang M, Gruber J. Hysteroscopy in the evaluation of patients with recurrent pregnancy loss: A cohort study in a primary care population. Surg Endosc 2004;18:1782-4.
19. Homer HA, Li TC, Cooke ID. The septate uterus: A review of management and reproductive outcome. Fertil Steril 2000;73:1-4.
20. Yu X, Yuhan L, Dongmei S, Enlan X, Tinchiu L. The incidence of post-operative adhesion following transection of uterine septum: A cohort study comparing three different adjuvant therapies. Eur J Obstet Gynecol Reprod Biol 2016;201:61-4.
21. AAGL Elevating Gynecologic Surgery. AAGL practice report: Practice guidelines on intrauterine adhesions developed in collaboration with the European Society of Gynaecological Endoscopy (ESGE). J Minim Invasive Gynecol 2017;24:695-705.
22. Guida M, Acunzo G, Di Spiezio Sardo A, Bifulco G, Piccoli R, Pellicano M, *et al*. Effectiveness of auto-crosslinked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic surgery: A prospective, randomized, controlled study. Hum Reprod 2004;19:1461-4.
23. Li X, Wu L, Zhou Y, Fan X, Huang J, Wu J, *et al*. New Crosslinked Hyaluronan Gel for the Prevention of Intrauterine Adhesions after Dilation and Curettage in Patients with Delayed Miscarriage: A Prospective, Multicenter, Randomized, Controlled Trial. J Minim Invasive Gynecol 2019;26:94-9.
24. Can S, Kirpinar G, Dural O, Karamustafaoglu BB, Tas IS, Yasa C, *et al*. Efficacy of a New Crosslinked Hyaluronan Gel in the Prevention of Intrauterine Adhesions. JSLS 2018;22. pii: E2018.00036.
25. Pabuçcu EG, Kovanci E, Şahin Ö, Arslanoğlu E, Yıldız Y, Pabuçcu R. New Crosslinked Hyaluronan Gel, Intrauterine Device, or Both for the Prevention of Intrauterine Adhesions. JSLS 2019;23. pii: E2018.00108.
26. Fei Z, Bin Z, Xin X, Fei H, Yuechong C. Meta-analysis on the use of hyaluronic acid gel to prevent recurrence of intrauterine adhesion after hysteroscopic adhesiolysis. Taiwan J Obstet Gynecol 2019;58:731-6.

Supplementary Table 1: Chinese scoring system of intrauterine adhesion

Item	Description	Score
Extent of the cavity involved	<1/3	1
	1/3-2/3	2
	>2/3	4
Pattern of adhesions	Filmy	1
	Fibrous	2
	Muscular	4
Tubal ostium	Both visualized	1
	Only one visualized	2
	Both not visualized	4
Endometrial thickness (advanced endometrial proliferation) (mm)	≥7	1
	4-6	2
	≤3	4
Menstrual pattern	<1/2 normal menstrual quantity	1
	Guttiform	2
	Amenorrhea	4
Abortion history	Artificial abortion	1
	Uterine curettage at first trimester	2
	Uterine curettage at second trimester	4
Gestation history	Spontaneous abortion	1
	Recurrent spontaneous abortion	2
	Infertility	4

Mild: 0-8, Moderate: 9-18, Severe: 19-28