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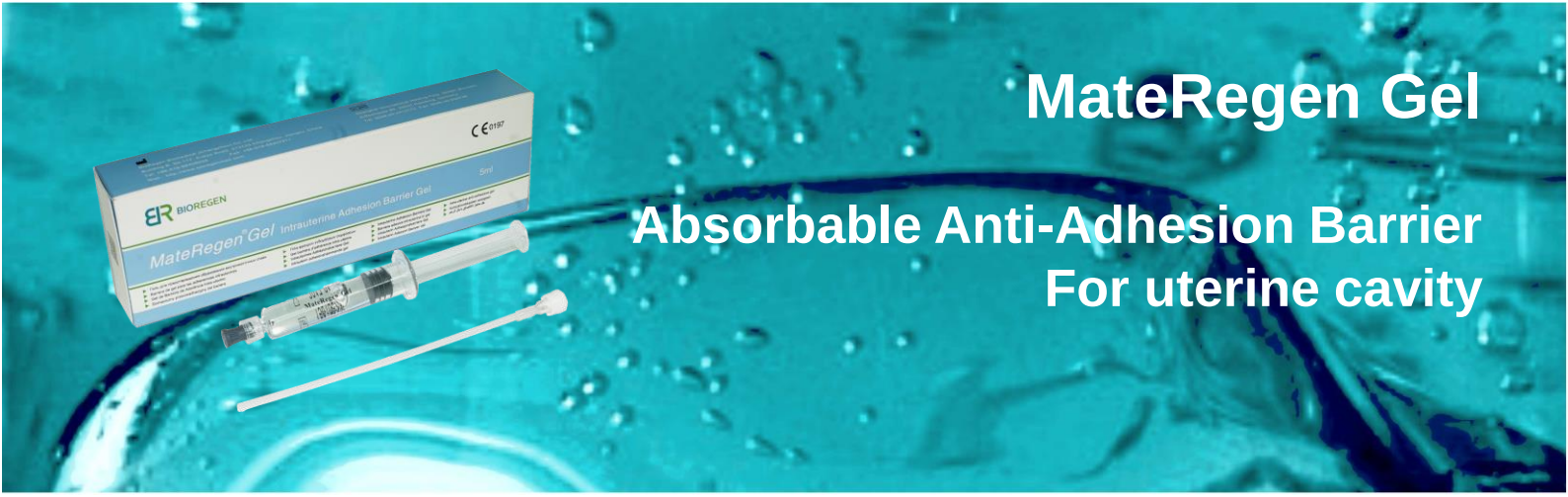

MateRegen Gel

Absorbable Anti-Adhesion Barrier
For uterine cavity

Novel crosslinked hyaluronan gel
Prevent Adhesion & Repair Injury

Improve endometrial quality
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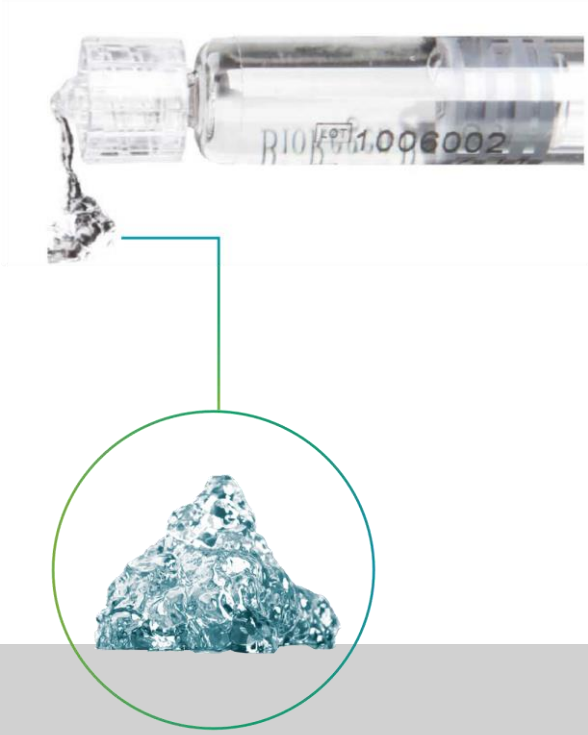

Safe

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Easy

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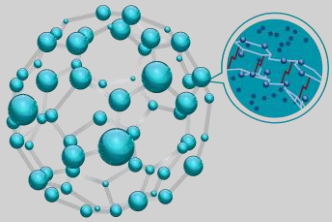

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A randomized multi-center controlled study on the efficacy and safety of a new crosslinked hyaluronan gel to prevent intrauterine adhesion following hysteroscopic adhesiolysis

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Introduction

Intrauterine adhesion (IUA) is one of the common disorders in OB/GYN practice. Any procedures that result in endometrium damages could possibly lead to IUA. In a cohort study, Taskin et al. (1) find that IUA formation after resection was present in 31.3% patients with solitary fibroids and 45.5% with multiple myomas. Guida et al. (2) find that the incidence of IUA after hysteroscopic resection of myoma, polyps and septa were 33.3, 18.2 and 37.5%, respectively. As abortion procedures reached 40-50 million worldwide at 2012 (3) and association between IUA and abortion was demonstrated (4), the prevalence of IUA would likely increase. Effective and safe interventions to prevent IUA after intrauterine procedures are therefore in urgent need.
Hysteroscopic adhesiolysis is currently a widely-performed procedure to remove the adhesions, restore the shape of uterine cavity, and ideally the functionality of endometrium. The major concern for this procedure is postoperative adhesion reformation. It was reported that adhesion reformation occurs in about 60% of severe cases (5). Preventing adhesion reformation after adhesiolysis is essential for a successful adhesiolysis procedure.
It has been reported that hyaluronic acid (HA) molecules could modulate inflammatory processes, regulate secretion of cytokines by macrophages, and facilitate scar-free tissue repair. However, due to its fluid nature and rapid *in vivo* degradation nature HA was not demonstrated to achieve a satisfactory efficacy to prevent post-operative adhesion (6). Crosslinking modification is an effective way to enable that HA material has high viscosity and degrades slowly so that it would stay in the application site and cover tissue surface during the critical tissue healing processes to prevent adhesion (7, 8). MateRegen® Gel is a new crosslinked HA gel that was developed using a proprietary chemical modification to the non-animal sourced HA material.
The objectives of this study were to explore the efficacy and safety of MateRegen® Gel in reducing IUA after hysteroscopic adhesiolysis for patients with moderate to severe IUA.

Methods

This study was approved by the Institutional Review Board and Ethical Committee. In total, 120 patients diagnosed with moderate to severe IUA according to the AFS scoring system (Table 1) (9) and underwent hysteroscopic adhesiolysis for the first time were recruited. All patients were informed consent and signed the Informed Consent Forms. Patients who were allergic to hyaluronan or its derivatives, with infection or malignant tumor of reproductive organs and with systemic diseases that could cause coagulopathy were excluded.
All patients were first examined by an experienced physician under hysteroscopy; the severity of the IUA was scored. Sharp hysteroscopic adhesiolysis with blunt tipped scissors under continuous saline flow was then performed. Upon completion of the adhesiolysis, patients were randomly assigned into

TABLE 1 - THE AMERICAN FERTILITY SOCIETY SCORING SYSTEM FOR IUA (1988).

Extent of cavity involved	<1/3	1/3-2/3	>2/3
	1	2	4
Type of adhesions	Filmy	Filmy and dense	Dense
	1	2	4
Menopausal pattern	Normal	Hypomenorrhea	Amenorrhea
	0	2	4
Stage I	Mild	1-4	
Stage II	Moderate	5-8	
Stage III	Severe	9-12	

treatment group (N=60) or to the control group (N=60). For patients in the treatment group a Foley balloon catheter (Perak, Malaysia) was first placed into the uterine cavity. Through the balloon port, 3ml Normal saline was injected into the balloon; through the urine drainage port; 2 ml of MateRegen® Gel (BioRegen Biomedical Co., Ltd., Changzhou, China) was then injected into the uterine cavity. For the control group, only Foley balloon catheter was placed into the uterine; 5ml Normal saline was injected into the balloon. The Foley balloon catheter was removed at the 4th day postoperatively for all patients.

Patients were followed-up at 3 days, 1 month, and 3 months postoperatively. Second-look hysteroscopic examination was performed 3 month postoperatively at 3-7 days after the completion of menstruation. The physicians who performed the second-look hysteroscopy were not aware of the study group assignment of the patients. After the IUA was evaluated and scored according AFS scoring system and recorded. IUA, if any, was then further lysed as needed per the physician's discretion.

The primary endpoint was the percentile of patients with zero AFS total score (Zero-AFS score rate) in each group. Secondary endpoint was AFS total score and score for each subcategory. Percentage of patients with different stages in each group was calculated and compared. The safety was evaluated based on the frequency of complications and severe events.

Data was statistically analyzed with SAS9.13 software (SAS Institute Inc.). The quantitative data was compared with two-tailed *student- t* test, ANOVA, and rank test; qualitative data was analyzed with c^2 test. $P< 0.05$ was considered as statistically different.

Results

Among the 120 patients, 5 in the treatment group and 4 in the control group were dropped off due to reasons unrelated with testing materials and treatment methods. Therefore, 111 patients completed this study, 55 in treatment group and 56 in control group.

The demographic characteristics, medical history, and AFS scores at the baseline were not significantly different between two groups.

Zero-AFS score rate in the treatment group is significantly higher than the control group (38.2 *vs* 16.1%, P = 0.0078; Figure 1). Using MateRegen® Gel resulted in significantly lower total AFS score, scores for the extent of cavity involved and the menopausal pattern than the control group ($p< 0.05$) (Table 2). The treatment group had significantly lower proportion of patients with moderate to severe adhesive stages than the control group ($p <0.05$) (Figure 1).

No complications, adverse events, and SAE related to the material and treatment were observed for both groups.

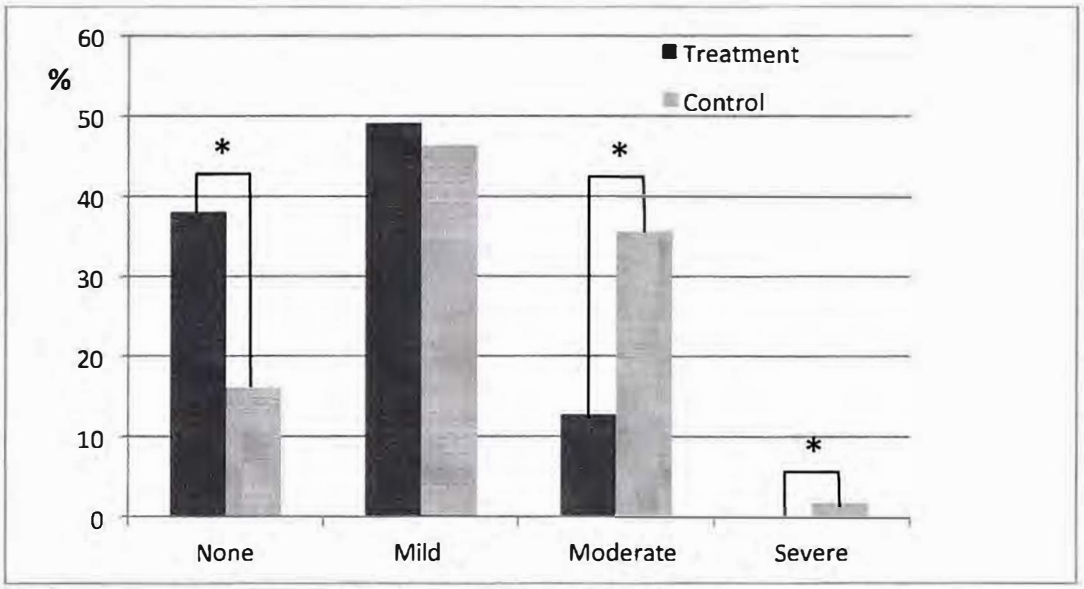

Figure 1 - Percentage of patients with different stages of IUA after treatment.
**** indicating significant differences between treatment and control group (p<0.05).***

TABLE 2 - THE SCORES OF IUA AT 3 MONTHS AFTER HYSTEROSCOPIC ADHESIOLYSIS (MEAN±SD).

Categories	Treatment group	Control group	*P* value
Extent of cavity involved	0.60 (0.74)	1.09 (1.08)	0.015
Type of adhesions	0.71 (0.85)	1.20 (1.26)	0.051
Menopausal pattern	0.80 (1.13)	1.39 (1.14)	0.005
Total score	2.11 (2.12)	3.68 (2.50)	0.001

Discussion

Only patients with moderate to severe IUA were enrolled in this study in order to evaluate the challenge situations dealt with during the clinical practice. Using of MateRegen® Gel significantly reduced reformation of IUA and its severity, and improved the endometrium function as shown by the normal menopausal pattern.

According to "Guidelines for treatment of IUAs" from AAGL (10), hysteroscopic adhesiolysis and use of anti-adhesion barrier are proposed to be the treatment choices. However, reformation of adhesion after adhesiolysis was observed in 60% of patients who initially had severe adhesion (2). Therefore, use of anti-adhesion barrier after adhesiolysis for those patients is obviously necessary. Formation of adhesion after surgery is associated with normal tissue healing processes where inflammatory reactions and re-vasculation of the repair tissue are physiological processes. HA has shown to modulate inflammatory reaction and reduce free-radicle production and scarring during tissue healing processes (11). However, nature HA material degrades too quickly *in vivo* and is not able to achieve the expected anti-adhesion efficacy.

Crosslink method was used to modify nature HA and improve its stability to prevent adhesions in abdominopelvic cavity and in uterine cavity. MateRegen® Gel is crosslinked hyaluronan that is from non-animal sources. The proprietary crosslinking technique improved the viscoelastic property meanwhile maintained the biological characteristics of natural HA molecules. This material is able to stay in the installation cavity for up to 14 days and cover the critical period of inflammatory phase during the wound healing (12). MateRegen® Gel could be also recommended for prophylactic application af-

ter intrauterine procedures that may cause injuries to endometrium.

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Original Article

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

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ABSTRACT **Study Objectives:** To evaluate the efficacy of a new crosslinked hyaluronan (NCH) gel in reducing the formation of intrauterine adhesions (IUAs) after dilation and curettage (D&C).

Design: Randomized controlled trial (Canadian Task Force classification I).

Settings: Six hospitals for maternal and child healthcare in China.

Patients: A total of 300 patients were randomized to undergo D&C for delayed miscarriage without previous history of D&C. Twenty-six patients (9%) were lost to follow-up and were excluded from the analysis.

Interventions: Women were randomly assigned to D&C alone (control group; n = 150) or D&C plus NCH gel application (NCH gel group; n = 150) with 1:1 allocation.

Measurements and Main Results: All patients were evaluated using the American Fertility Society classification of IUAs during follow-up diagnostic hysteroscopy, scheduled at 3 months after D&C procedure. The primary endpoint was the number of women with IUAs at 3 months, and the secondary endpoints were adhesion scores and severity of IUAs. Postoperative efficacy data were available for 274 women (137 in each group). Intrauterine adhesion formations were observed in 13 of the 137 women (9.5%) in the NCH gel group and in 33 of the 137 women (24.1%) in the control group (p = .0012; relative risk [RR], 0.3939; 95% confidence interval [CI], 0.2107–0.7153), a difference of 14.6% (95% CI, 5.92%–23.28%) between the 2 groups. The extent of intrauterine cavity involved, type of adhesion and menstrual pattern, and cumulative adhesion scores were significantly lower in the NCH gel group compared with the control group (p = .0007, .008, .0012, and .0006, respectively). The proportion of women with moderate to severe IUAs was significantly lower in the NCH gel group than that in the control group (1 of 137 [0.7%] vs 16 of 137 [11.7%]; p = .0002; RR, 0.0625; 95% CI, 0.0084–0.4648), a difference of 11.95% (95% CI, 5.39%–16.51%) between the 2 groups.

Conclusions: The current study demonstrates that IUAs are frequently formed after D&C for delayed miscarriage in women without a previous history of D&C procedures, and the application of NCH gel significantly reduces IUA formation. Journal of Minimally Invasive Gynecology (2018) ■■, ■■–■■ © 2018 AAGL. All rights reserved.

Keywords: American Fertility Society classification; Crosslinked hyaluronan gel; Hyaluronic acid gel

The authors declare that they have no conflicts of interest.

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Trauma to a gravid uterine cavity is known to be the main cause of intrauterine adhesions (IUAs), which occur in 1 of 5 women after miscarriage [1–4]. Considering the large number of miscarriages and terminations of pregnancy, with most treated by dilation and curettage (D&C), IUAs are a serious clinical problem and social issue. Approximately 15% to 20% of all clinically confirmed pregnancies end in miscarriage [3], and the annual number of abortions worldwide between 2010 and 2014 was estimated to be as high as 56.3 million [5], which may be the cause of more than 10 million IUAs annually. Although the clinical relevance of mild IUAs is unknown, moderate to severe IUAs are of concern and may have a significant impact on fertility and reproduction. In a systematic review and meta-analysis, 42% of pooled IUAs after miscarriage were found to be moderate to severe [3].

The etiology of IUA formation is multifactorial, making it important to identify preventive measures to avoid formation. A recent randomized controlled trial (RCT) evaluated the incidence of IUA after D&C in patients with a history of previous D&C [6]; however, the incidence of IUA after D&C in patients without previous D&C is not well determined, although this population is the majority experiencing miscarriage or termination of pregnancy [7–9].

Here we report the results of a prospective, multicenter RCT with a large number of patients to evaluate the incidence of IUAs, especially moderate to severe IUAs, after D&C in women without a history of previous D&C. The efficacy of a new crosslinked hyaluronan (NCH) gel (MateRegen; BioRegen Biomedical, Changzhou, China), a sterile, transparent, viscoelastic, and nonpyrogenic gel composed of highly purified crosslinked hyaluronan molecules, was also evaluated for the prevention of IUAs.

Materials and Methods

This prospective study, with a randomized, double-blind, parallel-group, controlled design, was conducted at 6 hospitals for maternal and child healthcare in China. The study protocol was approved by the Ethics Committee at each hospital. All participants were required to provide signed informed consent before participating. This study was registered at ClinicalTrials.gov (NCT03353909).

To minimize deviations in data owing to different types of miscarriage, only those patients with current delayed miscarriage were included in the study cohort. Inclusion criteria included age 18 to 45 years, no history of previous D&C, and undergoing D&C for current delayed miscarriage (gestational age no more than 20 weeks). All participants agreed to use adequate contraception throughout the follow-up period and to attend the follow-up examination according to the study protocol. Exclusion criteria for this study included known/suspected intolerance or hypersensitivity to hyaluronan gel or its derivatives; genital tract malformation; inflammation of the genital tract or pelvic cavity or clinical evidence of cancer in the genital tract; suspected genital tuberculosis; abnormal blood coagulation; history of peripheral vascular disease, alcohol/drug abuse, and/or mental illness; acute or severe infection; and autoimmune disease. Participants could voluntarily withdraw from the study for any reason at any time or be terminated by investigators owing to safety, violations of inclusion/exclusion criteria, and/or pregnancy.

The participants were randomly assigned to either D&C alone (control group) or D&C plus intrauterine NCH gel application (NCH gel group) in a 1:1 ratio. To avoid potential bias from surgeons, participant randomization and grouping were assigned only after the D&C procedure was completed. The study was not blinded to the surgeons, but the patients and the hysteroscopic examiners during follow-up were unaware of the group allocation of the patients under examination.

Surgical Procedure and Gel Application

All D&C procedures were performed by suction curettage under general anesthesia in accordance with procedural standards. In total, ten surgeons with minimum experience of 1000 procedures each performed the D&C procedures. The obtained tissues were sent for pathologic analysis at the discretion of the surgeon or according to local hospital guidelines. At the end of the D&C procedure, a syringe of NCH gel (3 mL) was inserted into the uterine cavity for patients assigned to the NCH gel group through a 15-cm sterile delivery cannula. NCH gel was not applied to the uterine cavity for patients in the control group.

A follow-up hysteroscopic examination was scheduled for 3 months (±7 days) after the D&C procedure at approximately 1 week after cessation of menstruation. Surgeons who performed the follow-up hysteroscopic examination did not participate in the D&C procedure and were not aware of the treatment that the patient received. Patients were also blinded to the treatment they received. A pregnancy test was performed before hysteroscopic examination. For patients with a positive pregnancy test, the hysteroscopic examination was canceled.

Findings on follow-up hysteroscopy were evaluated and recorded according to the American Fertility Society (AFS) classification (Supplementary Table S1) [10]. Hysteroscopic adhesiolysis was performed when adhesions were detected.

A follow-up survey was performed by all patients to record other treatments received, complications, and adverse events related to the D&C procedure and hysteroscopy, including postoperative complications, menstrual pattern, and use of contraception.

Endpoints

In this study, the primary endpoint was the number of women with IUA formation at the 3-month follow-up. Secondary endpoints included the extent of uterine cavity involvement, type of adhesions and menstrual pattern, cumulative adhesion scores, and severity of IUAs according

to the AFS classification [10]. Safety was evaluated based on complications and adverse events possibly related to the NCH gel application were recorded.

Statistical Analysis

The primary hypothesis in this study was that D&C plus NCH gel is superior to D&C alone, based on the primary assumption of an estimated IUA incidence of 30% in the control group and 15% in the NCH gel group. With a 2-tailed .05 significance level and 20% loss rate during follow-up, 300 patients with a 1:1 allocation would yield 80% power to detect this superiority.

All randomized women who started treatment were included in the intent-to-treat analysis. Continuous variables are expressed as mean ± standard deviation (SD) or as median (interquartile range), and categorical variables are expressed as count and percentage. The Student *t* test/Wilcoxon rank-sum nonparametric test and χ^2 test/Fisher exact test were used to check the homogeneity of baseline characteristics. The Wilcoxon rank-sum nonparametric test was used if variables did not follow a normal distribution and results were expressed as median (interquartile range). The Cochran–Mantel–Haenszel χ^2 test with a center effect adjustment was performed to estimate the difference in IUA incidence between the 2 groups. Analysis of covariance with center effect adjustment was performed to estimate the difference in IUA scores between the groups. All analyses were performed using SAS 9.13 (SAS Institute, Cary, NC), and a p value ≤.05 (2-tailed; $\alpha = 0.05$) was considered to indicate statistical significance.

Results

Between July 2016 and February 2017, 300 women were randomized into either the NCH gel group or the control group at 1:1 ratio. The NCH gel was applied in all women assigned to the NCH gel group (n = 150; 100%). Three hundred women constituted the full analysis set, as well as the safety population. A CONSORT flow chart of participants is shown in Figure 1. No women were withdrawn owing to adverse events. Twenty-six women did not undergo follow-up hysteroscopic examination because they did not return within the stipulated period; as a result, postoperative efficacy data were available for 274 women (137 in each group), who constituted the per protocol set.

Only patients who did not undergo previous D&C procedures were included in the study. Table 1 presents the baseline characteristics of the patients who completed the study. Age, gravidity, parity, and gestational age were comparable in the 2 groups (p = .6667, .3795, .3818, and .6728, respectively). One woman in the NCH gel group (transcervical resection of polyps) and 2 women in the control group (cesarean section) had undergone previous uterine surgery (p = .5701).

Blood loss during D&C was comparable in the 2 groups (11.37 ± 8.13 mL in the NCH gel group vs 10.81 ± 10.84 mL in the control group; p = .5743), and no signs of postoperative infection were reported in either group. No serious adverse events were observed during the study period, and there were no prolonged hospitalizations or reoperations owing to adverse events. Furthermore, no adverse events were attributed to the NCH gel treatment.

In each group, 137 of 150 women (91.3%) underwent the scheduled follow-up hysteroscopic examination. IUAs were observed in 13 of 137 patients in the NCH gel group, compared with 33 of 137 in the control group (9.5% vs 24.1%; p = .0012; risk ratio [RR], 0.3939; 95% confidence interval [CI], 0.2107–0.7153), a difference of 14.6% (95% CI, 5.92%–23.28%) (Fig. 2). The number needed to treat to benefit was 6.8 (95% CI, 4.3–19.9).

Adhesion scores are presented in Table 2. The subcategory adhesion scores of uterine cavity involved, type of adhesion, and menstrual pattern were all significantly lower in the NCH gel group compared with the control group (p = .0007, .008, and .0012, respectively). The mean cumulative adhesion score was also significantly lower in the NCH gel group (0.33 ± 0.106 vs 1.07 ± 2.06; p = .0006) (Table 2).

According to the AFS classification, 12 of the 13 IUAs (92.3%) observed in the NCH gel group were identified as mild and 1 IUA was moderate. In contrast, in the control group, 17 of 33 IUAs (51.5%) were mild and 16 (48.5%) were moderate. No patient had severe IUAs. The difference in IUA severity between the 2 groups was statistically significant (p = .0087).

In conclusion, moderate to severe IUAs were observed in 1 of 137 patients (0.7%) in the NCH gel group and in 16 of 137 patients (11.7%) in the control group (p = .0002; RR, 0.0625; 95% CI, 0.0084–0.4648), a difference of 11.95% (95% CI, 5.39%–16.51%). The number needed to treat to benefit was 9.1 (95% CI, 6.1–18.6).

Discussion

D&C procedures have been identified as 1 of the 2 most important risk factors for the development of IUAs, and the number of D&Cs is correlated with the severity of IUAs, which is linked to the risk of recurrent miscarriage [3]. Our present results show that the IUA formation frequently occurs even after only 1 D&C procedure for delayed miscarriage, consistent with data reported in the literature [2,3]. Comparing IUA formation in the current RCT with that found in a recent RCT reported by Hooker et al [6], the incidence of IUAs after more than 1 D&C procedure was higher than that after only 1 D&C procedure (odds ratio, 1.93), and the incidence of IUAs of moderate to severe grades was similar in the 2 circumstances (odds ratio, 1.58). However, the type of miscarriage (delayed or incomplete) experienced by patients enrolled in these 2 studies may affect this comparison [2,3].

Fig. 1

CONSORT flow diagram of participants.

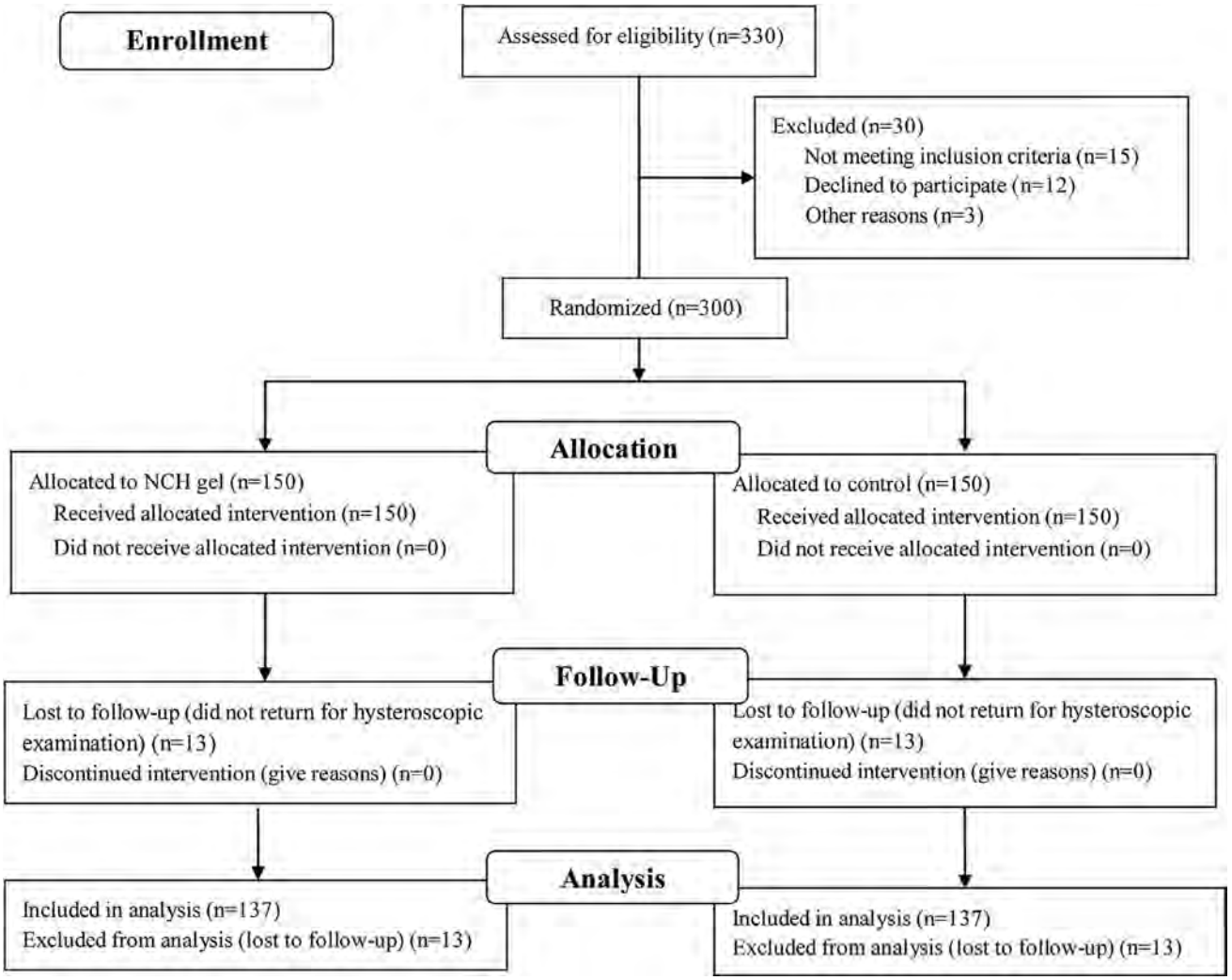
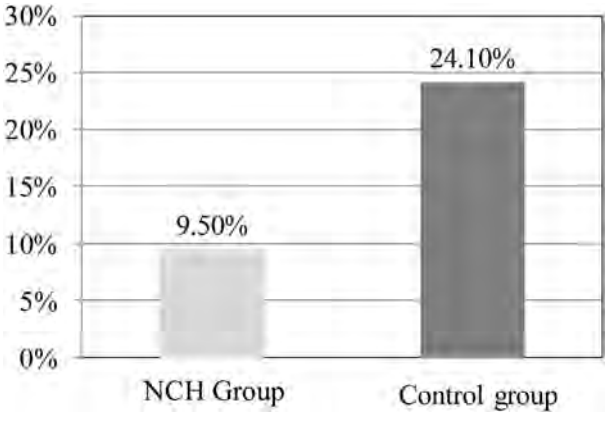


Fig. 2

The incidence of postoperative intrauterine adhesions (IUAs).



Surgical treatment of delayed miscarriage is more likely to result in IUA formation than incomplete miscarriage [2]. With respect to missed miscarriage, the period between fetal demise and D&C increases the likelihood of adhesion formation, possibly owing to fibroblastic activity of the remaining placental tissue [2]. On the other hand, no significant differences were detected in the pooled IUAs in patients with incomplete and delayed miscarriage in a meta-analysis of 1 cross-sectional study and 3 prospective cohort studies [3].

The objectives of IUA prevention are to maintain the normal size and shape of the uterine cavity, normal endometrial function, and fertility. Our present results clearly show that the application of NCH gel after D&C may significantly reduce the formation of IUAs, including moderate to severe IUAs, and it is reasonable to anticipate that NCH gel may have value in improving subsequent fertility and reproduction, as was shown in a preliminary consecutive case study.

Table 1

Baseline patient characteristics

Characteristic	NCH gel group (n = 137)	Control group (n = 137)	p value
Mean age, year ± SD	26.94 ± 4.72	26.84 ± 4.70	.6667
Age range, yr	17–44	19–45	
Gravidity, mean ± SD	1.17 ± 0.43	1.21 ± 0.43	.3795
Gravidity, n			
1	116	109	
2	20	27	
3	0	1	
4	1	0	
Parity, mean ± SD	0.11 ± 0.34	0.14 ± 0.37	.3818
Parity, n			
0	123	118	
1	13	18	
2	1	1	
Gestational age, wk, mean ± SD	9.33 ± 2.09	9.25 ± 2.27	.6728
Previous D&C, n	0	0	1.000
Previous intrauterine surgery, n (%)	1 (0.7%)	2 (1.4%)	.5701

D&C = dilation and curettage; NCH = new crosslinked hyaluronan; SD = standard deviation.

However, a well-designed study is warranted to confirm this expectation.

In human adults, the wound repair process commonly leads to a nonfunctioning mass of fibrotic tissue known as a scar [11–14]. Intrauterine trauma with disruption of the basalis layer may retard endometrial regrowth and lead to fibrotic tissue formation, resulting in endometrial sclerosis (fibrosis) and adhesion formation (the adherence of opposing surfaces by fibrotic tissue) [2]. The insertion of inert materials (e.g., intrauterine contraceptive devices, balloon catheter) may help to maintain the anatomic shape of the uterine cavity and reduce adhesion formation, but is unlikely to restore normal endometrial function.

Hyaluronan has been reported to have distinctive functions in scar-free wound healing by reducing inflammation and improving peritoneal reepithelialization [15]. However, owing to its fluid nature and rapid in vivo degradation, hyaluronan cannot persist sufficiently long to provide mechanical distention of the healing injuries during endometrial regrowth [16]. Therefore, natural hyaluronan is not suitable for adhesion prevention. Crosslinking modification is an effective way to improve in vivo persistence by increasing material viscosity and retarding degradation [17–19]. Therefore, in recent years, novel crosslinked hyaluronan gels have been successfully developed as absorbable adhesion barriers for intrauterine cavities [20,21]. Applied in the uterine cavity, these gels provide mechanical distention of the healing tissue during endometrial regrowth and also promote scar-free healing through the unique physicochemical properties and distinct biological functions of hyaluronan.

Table 2

Patient adhesion scores and severity of IUAs at follow-up hysteroscopic examination

Parameter	NCH gel group	Control group	p value
Adhesion scores, mean ± SD	n = 137	n = 137	
Extent of cavity involved	0.09 ± 0.29	0.32 ± 0.62	.0007
Type of adhesions	0.10 ± 0.33	0.33 ± 0.63	.0008
Menstrual pattern	0.13 ± 0.50	0.42 ± 0.89	.0012
Cumulative	0.33 ± 0.106	1.07 ± 2.06	.0006
Severity of IUAs, n (%)*	n = 13	n = 33	.0087
Stage I (mild)	12 (92.3)	17 (51.5)	
Stage II (moderate)	1 (7.7)	16 (48.5)	
Stage III (severe)	0 (0)	0 (0)	

IUA = intrauterine adhesion; NCH = new crosslinked hyaluronan; SD = standard deviation.
* Severity is based on the cumulative score of the American Fertility Society classification.

This large, multicenter RCT examining the formation and prevention of IUAs after D&C for delayed miscarriage in women without a history of previous D&C has several strengths. The participants and hysteroscopic examiners were blinded to treatment assignment during follow-up. More than 90% of the participants completed the study, and the number of patients lost to follow-up was limited. Potential limitations of this study include the weakened generalizability owing to the all-Chinese population and lack of racial diversity in the study cohort, the short duration (3 months), and the lack of data regarding impacts on fertility and long-term clinical symptoms.

In conclusion, this study demonstrates that IUAs are frequently observed after D&C for delayed miscarriage in women without previous D&C, and that the application of NCH gel in the uterine cavity after D&C significantly reduces incidence and severity of IUAs and potentially facilitates endometrial function, as evidenced by an improved menstrual pattern.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jmig.2018.03.032.

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Supplementary Table 1

The American Fertility Society (AFS) classification of intrauterine adhesion (1988)

Extent of cavity involved	<1/3	1/3–2/3	>2/3
Score	1	2	4
Type of adhesions	Filmy	Filmy and dense	Dense
Score	1	2	4
Menstrual pattern	Normal	Hypomenorrhea	Amenorrhea
Score	0	2	4

Prognostic classification of disease severity: Stage I (mild) cumulative score 1–4; Stage II (moderate) cumulative score 5–8; Stage III (severe) cumulative score 9–12.

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Using New-Crosslinked Hyaluronic Acid Gel to Prevent Intrauterine Adhesion After Hysteroscopic Septum Resection: A Prospective, Randomized, Controlled Study

Histeroskopik Septum Rezeksiyonu Sonrası İntrauterin Adezyonu Önlemede Yeni Çapraz Bağlı Hyaluronik Asit Jel: Prospektif, Randomize Kontrollü Çalışma

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ABSTRACT

Objective: A prospective, randomized, controlled study was performed to assess the effect of new-crosslinked hyaluronic acid (NCHA) gel on the reoperation rates of women who underwent hysteroscopic septum resection. **Material and Methods:** A total of 45 infertile women who underwent hysteroscopic septum resection were randomly assigned to two groups as group with new-crosslinked hyaluronic acid (NCHA) gel applied following septum resection (n=23) and group without hyaluronic acid gel (n=22) but Foley catheter insertion into the cavity, groups were assessed 3 months later whether the postoperative uterine cavity was appropriate for embryo implantation and normal pregnancy. Uterine adequacy was determined according to the presence of remnant septum and adhesion formations. **Results:** There was a significant difference between groups in terms of rate of reoperation indicated for remnant septum resection or adhesiolysis of the previously resected septum site (1/23 versus 7/22, P<0.05). **Conclusion:** Our data showed that application of new-crosslinked hyaluronic acid (NCHA) gel following hysteroscopic septum resection is associated with significantly higher rate of surgical success in women with uterine septum.

Keywords: Uterine septum; hysteroscopy; intrauterine adhesion; new-crosslinked hyaluronic acid gel

ÖZET

Amaç: Yeni çapraz bağlı hiyaluronik asit jelinin, histeroskopik septum rezeksiyonu uygulanan kadınların reoperasyon oranlarına etkisini değerlendirmek için prospektif, randomize, kontrollü bir çalışma yapıldı. **Gereç ve Yöntemler:** Histeroskopik septum rezeksiyonu uygulanan toplam 45 kısır kadın, septum rezeksiyonu sonrası hyaluronik asit jeli uygulanan (n = 23) ve hyaluronik asit jeli olmaksızın Foley kateter uygulanan (n = 22) hastalar olmak üzere iki gruba randomize edildi. Gruplar 3 ay sonra postoperatif uterus kavitesinin embriyo implantasyonu ve normal gebelik için uygun olup olmadığı açısından değerlendirildi. Uterin kavite yeterliliği, kalan septum ve adezyon formasyonlarının varlığına göre belirlendi. **Bulgular:** Gruplar arasında rezidüel septum rezeksiyonu ya da daha önce rezeke edilen septum alanın adeziyolizisi ile ilişkili reoperasyon oranı açısından gruplar arasında anlamlı fark vardı (1/23'e karşı 7/22, P<0,05). **Sonuç:** Verilerimiz, histeroskopik septum rezeksiyonu sonrası hyaluronik asit jeli uygulamasının, uterus septumlu kadınlarda anlamlı olarak daha yüksek cerrahi başarı oranı ile ilişkili olduğunu göstermiştir.

Anahtar Kelimeler: Uterin septum; histeroskopi; intrauterin adezyon; hyalurinan jel

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Intrauterine adhesions are the most commonly encountered chronic complications following operative hysteroscopy.[1,2] Variable rates have been reported and depend on the complexity of the surgical intervention ranging between 4 to 45%.[3] Severity of the condition has been defined according to the ostial visibility and the presence of menstrual bleeding, using AFS or ESGE classification systems.[4] Complete obliteration of the whole uterine cavity, the Asherman syndrome, is a serious issue presenting with secondary amenorrhea.[5] Moreover some other severe consequences have been introduced such as placental adhesion anomalies in the following pregnancies.[6] Hysteroscopy is the most commonly suggested tool to diagnose and treat these complications.[6]

Some anti-adhesive materials have been used to prevent postoperative adhesions.[7] Hyaluronic acid gel has been studied to prevent intrauterine adhesions and favorable fertility outcomes have been reported by studies on rabbits.[8-10]

Our study was performed to assess the effect of new-crosslinked hyaluronic acid (NCHA) gel on the reoperation rates of women who underwent hysteroscopic septum resection.

MATERIAL AND METHODS

This prospective randomized study was approved by the institutional review board of our hospital, Zeynep Kamil Women and Children's Health, Training and Research Hospital and carried out at the IVF department between January 2016 and March 2017.

A total of 45 infertile women with a diagnosis of uterine septum by prior hysterosalpingography were randomly assigned to two groups by choosing themselves, a closed envelope which contains the selected group written in it and underwent hysteroscopic septum resection (Table 1). Before the surgery, history of the menstrual pattern, previous intrauterine interventions and reproductive history and written consent were obtained from each participant. All women underwent transvaginal sonographic evaluation. We excluded the cases with additional interventions to the septum resection, systemic disorders and cases with any other intracavitary pathology.

Hysteroscopic interventions were performed under general anaesthesia for uterine septum resection. The operation was carried out by one of three reproductive surgeons in the same department with the use of similar techniques.

A 4.5 mm hysteroscope (Storz, Germany) and the loop electrode were used for resection. Following the complete resection of uterine septum, we applied 5 ml new-crosslinked hyaluronic acid (NCHA) gel (MateRegen gel, Bioregen Biomedical Co.) to the patients randomized in the first group (n=23) and in the second group (n=22) we inserted a Foley catheter into the uterine cavity and inflated it with 3 cc of serum physiologic, in the immediate postoperative period.

All patients had prophylactic antibiotherapy (100 mg doxycycline BID) for 5 days and 2 cycles of Estrogen 2 mg BID for 25 days plus 5 mg MPA in the last 10 days, for endometrial regeneration. For women who had an intrauterine Foley catheter inserted, the device was removed after 7 days as an outpatient procedure.

Both groups were assessed by a second-look hysteroscopy planned for each case 3 months later in the early proliferative phase; whether the postoperative uterine cavity was appropriate for embryo implantation and normal pregnancy. During the second look hysteroscopy following overall inspection to document the extent and severity of any intra-uterine adhesions, patients were evaluated for further intervention to resect remnant uterine septum or adhesiolysis, if needed. Uterine adequacy was determined according to the presence of remnant septum or adhesion of the previously resected septum site.

STATISTICAL ANALYSIS

Data were analyzed using SPSS 15.0 for Windows. Fisher's exact test was used to compare rate of necessity of reoperation due to the postoperative intrauterine adhesions. P value <0.05 was accepted to be statistically significant.

RESULTS

We found that there were 7 patients in the Foley catheter group who need reoperation for adhesiolysis of the previously resected septum site vs only 1 in the

TABLE 1: Second look hysteroscopy findings.

	45 infertile women		
	Hyaluronan (n=23)	Foley Catheter (n=22)	p
Post-op Adhesions	1	7	<0.05
Remnant Septum	0	0	NS

new-crosslinked hyaluronic acid (NCHA) gel group. There was any remnant septum in both groups.

The AFS score of post op adhesions are shown on the Table 2. The difference between these two groups, in terms of rate of reoperation was statistically significant (1/23 versus 7/22, $p<0.05$).

DISCUSSION

In our study, we tried to assess the efficacy of new-cross linked derivative of hyaluronic acid (NCHA) to prevent postoperative adhesion following uterine septum resection. Our data showed that the intrauterine application of new-crosslinked hyaluronic acid (NCHA) gel, just after the surgical intervention, may be superior to the conventional techniques. As previous studies indicated, the major long-term complication that all surgeons try to avoid during resectoscopic surgery is post-operative adhesions.[3] Due to the high frequency of intrauterine adhesions after resectoscopic surgery, clinicians look for new approaches to prevent these complications.[3] Some measures have been introduced to prevent intrauterine adhesions.[12-15] In the first studies, auto-cross linked derivative of hyaluronic acid was shown to reduce reformation of intrauterine adhesions after hysteroscopic adhesiolysis.[15] Following recent studies confirmed earlier findings and pointed the safety and effectiveness of this agent to improve women's health, reducing the need for re-intervention after hysteroscopic surgery due to post-operative intrauterine adhesion formation.[16]

Accumulated data were presented by two recent metaanalyses. In one of the meatanalyses Healey indicated a lack of definitive evidence to conclude that any treatment is effective in preventing posthysteroscopy uterine adhesion formation, the heterogeneity and a high risk of bias to make any definitive conclusion.[17]

In the second metaanalyses, Mais showed a lower incidence of postoperative adhesions in patients who received hyaluronan gel compared to patients who underwent standard surgery only, but authors pointed the necessity of further RCTs to assess the efficacy of auto-crosslinked hyaluronan gel.[18]

In conclusion, the data of our study showed that the application of new-crosslinked hyaluronic acid (NCHA) gel following hysteroscopic septum resection is associated with significantly higher rate of surgical success in women with uterine septum. Then we strongly recommend the use of it.

TABLE 2: Severity of post-op adhesions.

	Post-op Adhesions-AFS score	
	Hyaluronan (n=23)	Foley Catheter (n=22)
1	3	3
2	-	3
3	-	6
4	-	2
5	-	4
6	-	2
7	-	2

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SCIENTIFIC PAPER JSLS

Efficacy of a New Crosslinked Hyaluronan Gel in the Prevention of Intrauterine Adhesions

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ABSTRACT

Background and Objectives: The authors sought to assess the effect of the use of a new crosslinked hyaluronan (NCH) gel on the prevention of intrauterine adhesions (IUAs) in women underwent curettage in the second trimester.

Methods: Between June 2016 and September 2017, 60 patients who underwent curettage for retained placental tissue after medically induced or spontaneous pregnancy loss in the second trimester were enrolled in the study. The patients were randomly assigned to 1 of 2 groups: Group 1 patients received curettage plus NCH gel (intervention group), and group 2 patients received curettage alone (control group). The main outcomes were the rate and severity of IUA formation, which were assessed by follow-up hysteroscopy performed in the ensuing 2–6 months.

Results: The hysteroscopic findings were available for 20 patients in group 1 and 28 patients in group 2. IUAs were observed in 6 patients in group 2, while no IUAs was observed in group 1 ($P = .007$). IUAs were staged as mild in 4 patients (14.28%) and moderate in 2 patients (7.14%) in group 2 according to the American Fertility Society classification of IUAs.

Conclusions: Our study demonstrates that NCH gel appears to be able to reduce the formation of IUAs in women who undergo curettage in the second trimester, although larger controlled, randomized, multicenter studies are needed to confirm these results.

Key Words: Intrauterine adhesions, Miscarriage, Termination of pregnancy, Dilatation and curettage, Hyaluronic acid.

INTRODUCTION

Intrauterine adhesions (IUAs) are fibrous adhesive bands causing partial or complete obliteration of the uterine cavity.[1,2] IUAs are believed to develop after a intrauterine operation that damages the basalis layer of the endometrium.[3] Curettage after abortion or postpartum is the procedure most commonly reported as an underlying cause,[1] probably due to gestational changes in the uterus and low estrogen status after the intervention.[4] Although IUAs can be asymptomatic, they may result in menstrual disorders, infertility, and obstetric complications.[1,5] The term *Asherman syndrome* is used in the presence of IUAs combined with signs and symptoms such as menstrual disturbance, pain, and subfertility.[6] Hysteroscopy has been considered to be the most reliable diagnostic method for the diagnosis of IUAs. It provides an accurate description of localization and the extent and type of adhesions vi direct vision of the uterine cavity.[6]

A recent meta-analysis reported the prevalence of IUAs after dilatation and curettage (D&C) for a first-trimester miscarriage to be 19%, with 42% of the IUAs being moderate to severe.[7] Among patients who underwent curettage after a pregnancy loss, more advanced gestation and increasing size of the uterine contents are associated with an increased risk of IUAs.[8,9] Multiple procedures or the use of sharp curettage can also result in increased prevalence of IUAs.[6,7]

Crosslinked hyaluronan gel is an absorbable adhesion barrier that can be applied to the uterine cavity to keep the healing tissues separated during the critical repair phase after uterine surgery for the prevention of IUAs.[4] IUAs may also develop after hysteroscopic procedures,[10] and intrauterine crosslinked hyaluronan gel application has been showed to reduce the severity of postoperative ad-

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hesions after hysteroscopic procedures.[11,12] A recent randomized controlled trial (RCT) that compared the effect of crosslinked hyaluronan gel on IUA formation after D&C for first-trimester miscarriage in women with a history of at least one D&C also revealed reduction in the incidence and severity of IUAs.[13] There is a scarcity of data regarding the effect of crosslinked hyaluronan gel on IUA formation after curettage specifically performed in the second trimester or postpartum.

A new crosslinked hyaluronan (NCH) gel (MateRegen® gel; BioRegen BioMedical Co., Changzhou, China) that is gradually absorbed within 1 to 2 weeks due to its much higher viscosity than natural hyaluronan was recently developed to use in the prevention of IUAs after uterine surgery. Therefore, the objective of this prospective, randomized, controlled study was to evaluate the effectiveness of this NCH gel in the prevention of IUA development as assessed by hysteroscopy in a specific group of patients who underwent curettage for retained placental tissue after medically induced or spontaneous pregnancy loss in the second trimester.

METHODS

This randomized controlled study was conducted in a tertiary referral center—the Department of Obstetrics and Gynecology at Istanbul University School of Medicine. The study protocol was approved by the Central Ethics Committee of the Ministry of Health of Turkey (112616–14991). Between June 2016 and September 2017, patients who had medically induced or spontaneous pregnancy loss and required curettage afterward who were at least 18 years old with a gestational age between 14 and 28 weeks were invited to participate in this study.

The surgical evacuation of the uterus with sharp curettage is performed under local anesthesia when the placenta fails to separate within 30 minutes or is incompletely delivered. Abortion in Turkey is legal until the 10th week after conception unless there is fetal or maternal indication. Therefore, all termination-of-pregnancy procedures, using vaginal misoprostol, were performed for fetal and maternal indications such as fetal anomaly, preterm premature rupture of membrane, or early-onset severe preeclampsia among these patients. Exclusion criteria were a history of previous D&C or any other intrauterine surgery such as diagnostic or operative hysteroscopy, the presence of a known uterine anomaly, and having signs of active infection. Maternal age, gestational week, obstetric history, and indications for medically induced abortion were analyzed.

The patients who met all of the inclusion criteria and none of the exclusion criteria and who provided written informed consent after the purpose of the protocol was clearly explained were randomly assigned into group 1 (intervention group) or group 2 (control group). At the end of the curettage procedure, group 1 underwent intrauterine application of 5 mL NCH gel (MateRegen® gel), whereas nothing was applied to the uterine cavity in group 2 patients. The presence and severity of IUAs were assessed with office hysteroscopy performed in the ensuing 2–6 months after the procedure by nonblinded surgeons for group assignment who also performed the curettage. None of the patients had any intrauterine intervention between the 2 procedures.

The diagnostic hysteroscopy was performed during the proliferative phase, usually within 5 days after the end of menstruation, by using a 5-mm instrument (Karl Storz Endoscope) without anesthesia. This hysteroscopic system has specialized channels in the metal sheath surrounding the telescope that serve for irrigation and suction and insertion of surgical equipment, such as biopsy forceps and scissors. The uterine cavity was entered without cervical dilatation by using the no-touch technique. With this technique, the vagina was entered with the hysteroscope, and the uterine cavity was entered vi the following anatomical pathway: cervix to external os to cervical canal to internal os. Normal saline solution (NaCl 0.9%) was used for uterine distention. Hysteroscopic findings were thoroughly recorded on a dedicated form. The severity of IUAs was assessed by using the American Fertility Society (AFS, 1988) classification system of IUAs.[14] When IUAs were identified during the study, adhesiolysis was performed by using the hysteroscopic scissors if the IUAs were not ruptured by distention or the hysteroscope sheath.

Statistical analysis was performed with JMP software version 10.0.0 (SAS, Cary, NC, USA). Patient characteristics were analyzed via descriptive statistics. For continuous variables, the mean ± SD or median and range were calculated. For categorical variables, the numbers and percentages in each category were recorded. Differences between parameters were compared by use of the Student *t* test. Frequency distributions were compared with use of the χ^2 test. $P < .05$ was considered statistically significant, and all of the performed tests were 2-sided.

RESULTS

The CONSORT flow chart of participants is given in **Figure 1**. Of the 60 patients who enrolled in the study, 29

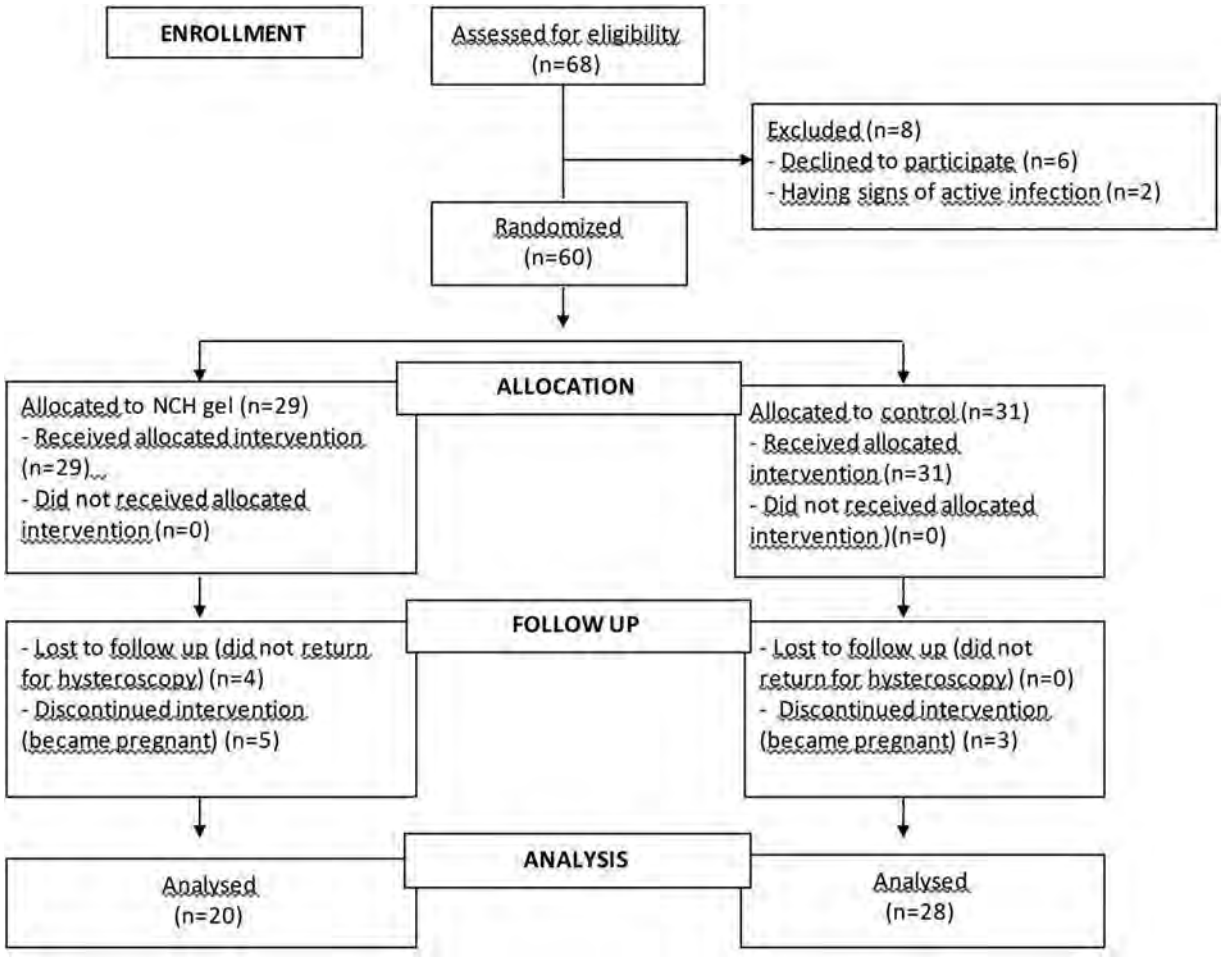

Figure 1. CONSORT flow diagram of participants.

patients were randomly assigned to group 1 (intervention group) and 31 patients were randomly assigned to group 2 (control group). Four patients in group 1 were loss to follow-up. Also, 5 patients in group 1 and 3 patients in group 2 became pregnant during the period between the curettage performance and follow-up hysteroscopy. Therefore, a total of 48 patients underwent follow-up hysteroscopy: 20 (69%) in group 1 and 28 (90%) in group 2.

Characteristics of patients included in the study are given in **Table 1**. The mean gestational age at the time of abortion was 19.03 weeks and 20.03 weeks in group 1 and group 2, respectively ($P = .25$). There was no significant difference in maternal age between group 1 and group 2 (30.1 [SD 5.27] vs 28.8 [SD 6.34] years; $P = .41$). Gravidity and parity were also comparable in groups 1 and 2 (2.1 vs 2.32; $P = .56$, and 0.65 vs 0.9; $P = .39$, respectively). None of the patients included in the study had a history of prior uterine surgery other than cesarean section. One patient in group 1 and 2 patients in group 2 had a spontaneous incomplete abortion in the second trimester; other patients in both groups underwent the termination of pregnancy with vaginal misoprostol. Indications for termination of pregnancy are given in **Table 2**. All of the patients in both groups had no clinical symptoms of Asherman syndrome, such as menstrual disturbance or pelvic pain, after the curettage.

While no IUAs were observed in group 1 patients, IUAs were observed in 6 group 2 patients at follow-up hysteroscopy (0% vs 21.43%; $P = .007$). When the IUAs detected in the group 2 were evaluated according to AFS, they were staged as moderate in 2 patients (7.14%) and as mild in 4 patients (14.28%). The findings of follow-up hysteroscopy are shown in **Table 3**. The mild adhesions were ruptured via distention or the hysteroscope sheath, whereas adhesiolysis was performed by using the hysteroscopic scissors

Table 1.
Characteristics of Patients

Parameter	Group 1	Group 2	*P* value
Age, year (mean ± SD)	30.1 ± 5.27	28.87 ± 6.34	.41
Gestational age, week (mean ± SD)	19.03 ± 3.61	20.03 ± 3.15	.25
Gravidity, n (mean ± SD)	2.10 ± 1.20	2.32 ± 1.66	.56
Parity, n (mean ± SD)	0.65 ± 0.20	0.90 ± 0.20	.39
Type of pregnancy loss, n			
Termination of pregnancy	28	29	
Spontaneous abortion	1	2	

Table 2.
Findings of Follow-up Hysteroscopy

Extent of IUAs According to AFS	Group 1	Group 2	*P* value
IUAs, n	0	6 (21%)	.007
Stage I (mild)		4 (14%)	
Stage II (moderate)		2 (7%)	

AFS = American Fertility Society; IUA = intrauterine adhesion.

Table 3.
Indications for Termination of Pregnancy

Parameter, n	Group 1	Group 2
Fetal anomaly	12	14
Twin-twin transfusion syndrome	1	—
Preterm premature rupture of membrane	9	9
Early-onset preeclampsia	2	—
Intrauterine fetal death	4	4

for moderate adhesions. No complications or adverse events associated with intrauterine application of gel were reported in the intervention group, and no complications related to curettage or follow-up hysteroscopy were observed in either group.

DISCUSSION

IUAs are a major long-term complication of intrauterine surgery, and almost 90% of cases are related to surgical evacuation of products of conception.[1] Application of intrauterine materials to keep the uterine walls separate have been used in attempts to reduce of the occurrence of IUAs. A new category of adhesion prevention methods is the use of biologic barriers,[15] and one such derivative is crosslinked hyaluronan gel. According to a recent systematic review that included 3 RCTs, the use of crosslinked hyaluronan gel after operative hysteroscopy is associated with a reduced IUA rate at second-look hysteroscopy compared with no treatment (odds ratio [OR] 0.41, 95% confidence interval [CI] 0.22–0.77, $P = .006$).[13] A study in animals showed improved fertility with the use of immediate postoperative crosslinked hyaluronan gel after high-risk intrauterine surgery.[16]

Limited data are available regarding the use of biologic barriers after pregnancy-related curettage in the first trimester. A recent multicenter RCT that included 152 women with a miscarriage within 14 weeks with at least 1 previous D&C for miscarriage or termination of pregnancy reported that intrauterine application of crosslinked hyaluronan gel after conventional D&C reduces the cumulative rate and severity of IUAs.[17] And the only previous RCT of the use of biologic barrier after surgical abortion showed that Seprafilm, another biologic barrier of chemically modified hyaluronic acid and carboxymethylcellulose, prevents the occurrence and reduces the severity of endocervical or endometrial adhesions.[18] In accordance with previous studies, our results show that intrauterine application of crosslinked hyaluronan gel after surgical evacuation of uterus appears to be safe and reduces the incidence of IUAs. In the study, a recently developed NCH gel with prolonged absorption time to 1–2 weeks was used. Therefore, this NCH gel may continue to be effective in the first 5–7 days, which is thought to be the critical time for IUAs to develop.

This study included a specific group of patients who are thought to be more likely to have postsurgical IUAs based on the assumption that more advanced gestational age and increased size of the uterine contents can be associated with an increased trauma to the basal endometrial

layers and risk of IUAs due to the need for more prolonged or vigorous efforts for evacuation.[8,9] The incidence of IUAs reported in the control group of the study was consistent with previous reports. In a recent systematic review and meta-analysis, patients were evaluated with hysteroscopy within 12 months after miscarriage and IUAs were reported in 183 of the 912 women, resulting in a pooled prevalence of 19.1% (95% CI 12.8–27.5%). The extent of IUAs was mild in 58% and moderate to severe in 42%.[7] In a prospective cohort study conducted by Kajanoja et al,[19] among 395 nulliparous women between 13 and 20 weeks who underwent termination of pregnancy via intra-amniotic prostaglandin induction and then D&C, IUAs were detected in 28 (16.2%) of 173 women who were evaluated by hysterosalpingography at 5–8 months after the surgical procedure.

Surgical management of termination of pregnancy and of spontaneous and incomplete abortions is a known major risk factor for the development of IUAs and Asherman syndrome.[3,6,7,20] In the systematic review and meta-analysis in which IUAs evaluated by hysteroscopy within 12 months after miscarriage, no IUAs were identified in women treated with expectant or medical management.[7] For the prevention of IUA development, trying to manage the cases with expectant or medical management should also be considered when possible.

We are not aware of any previous study evaluating the effect of intrauterine application of a biologic barrier on IUA development in women who underwent pregnancy-related curettage in the second trimester. This is a specific group of women with an increased risk for IUAs. The protocol allowed us to exclude patients with a history of previous D&C or any other intrauterine surgery. Therefore, IUA formation detected during follow-up hysteroscopy could be attributed to the pregnancy loss or its treatment. For the patients in our study, the presence and the severity of IUAs were prospectively evaluated with hysteroscopy, which is considered the gold standard for IUA detection,[21,22] and were graded according to one of the accepted classification systems.[14]

This RCT has certain limitations, as it was a nonblinded study in a small population. The same group of surgeons performed the curettage and follow-up hysteroscopy so they could not be blinded for group assignment. Also, placebo for intrauterine application was not available in the control group. Another limitation was the higher rate of patients who were loss to follow-up in group 1 and the patients who could not undergo hysteroscopy due to becoming pregnant during the period between abortion and follow-up hysteroscopy, which was observed at a higher rate in the intervention group.

Finally, the effect of NCH gel on long-term fertility and reproductive outcome was not assessed as main outcomes in our study, although the pregnancy rate after curettage was higher in the intervention group. Because IUAs detected during follow-up hysteroscopy were treated, we do not believe that it can be relevant to compare reproductive outcomes with a longer follow-up of the included patients. The relationships between IUAs and secondary infertility miscarriages, ectopic pregnancy, abnormal placentation, fetal growth restriction, fetal anomalies, premature delivery, and postpartum hemorrhage have been reported[1,5,23]; however, the impact of these largely asymptomatic cases of IUAs on fertility and reproductive outcomes has been not clearly defined. Larger studies with a longer follow-up are needed to determine the effect of intrauterine application of NCH after surgical evacuation of products of conception on subsequent fertility, reproductive, and obstetric outcomes.

Although not definitive, our RCT demonstrates that NCH gel appears to be able to reduce the formation of IUAs in women with intrauterine gel application after curettage for retained placental tissue after medically induced or spontaneous pregnancy loss in the second trimester. Considering the high frequency of IUAs developed after surgical evacuation and possible adverse long-term outcomes of this procedure in women who tend to be young and in their early reproductive life, the application of NCH gel may be considered a safe and effective strategy for the prevention of IUAs. However, larger controlled, randomized, multicenter studies are needed to confirm these results.

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SCIENTIFIC PAPER JSLS

New Crosslinked Hyaluronan Gel, Intrauterine Device, or Both for the Prevention of Intrauterine Adhesions

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ABSTRACT

Background and Objectives: To compare the efficacy of 3 different techniques for prevention of adhesion reformation after hysteroscopic adhesiolysis in patients with moderate-to-severe intrauterine adhesions. Short-term assisted reproductive outcomes were also compared.

Study Design: Total of 72 cases were randomized to Lippes loop intrauterine device (IUD) only, IUD plus a new crosslinked hyaluronan (NCH) gel, or NCH gel only following hysteroscopic adhesiolysis. All cases received hormonal therapy and a second hysteroscopy was carried out. Endometrial thickness values were measured using transvaginal ultrasonography and American Fertility Society adhesion scores were noted during first and second hysteroscopy in all groups. Reproductive outcomes were also compared for those who received in vitro fertilization treatment.

Results: Transvaginal ultrasonography revealed significantly better endometrial thickness in the IUD+NCH (7.5 mm) and NCH-only groups (6.5 mm) than the IUD-only group (5 mm) ($P < .001$). All groups revealed enhanced but comparable American Fertility Society adhesion scores on second-look hysteroscopy. A total of 37 patients received in vitro fertilization treatment after surgical management of adhesions. Ongoing pregnancy rates after in vitro fertilization were 27%, 40%, and 36% in IUD, IUD+NCH, and NCH groups, respectively. However, the difference between the groups did not reach statistically significant difference.

Conclusion: All interventions are of similar efficacy in the prevention of adhesion reformation after hysteroscopic adhesiolysis for moderate to severe intrauterine adhesions. However, better endometrial thickness values were observed in those who received NCH gel either alone or in combination with IUD. Assisted reproductive outcomes of both groups were comparable for ongoing pregnancy rates.

Key Words: Adhesion, Asherman, Gel, Hysteroscopy, IVF.

INTRODUCTION

Intrauterine adhesion (IUA) formation is one of the most challenging issues in gynecology practice resulting in infertility, recurrent miscarriages, or menstrual abnormalities.[1] It occurs in 1.5% to 3% of infertile women and in up to 40% of women after recurrent dilatation and curettage (D/C) for miscarriage.[1] Moderate-to-severe intrauterine adhesions (IUAs) may greatly impact the fertility potential of affected women. Trauma to the basal layer of the endometrium is regarded as the primary initiating factor for adhesion formation.

Hysteroscopy has been the most effective method for diagnosis and treatment. It does not only offer magnification but also allows direct view of the adhesions; therefore, allowing for a precise and safe treatment. Despite favorable outcomes, adhesion recurrence is one of the most challenging issues complicating nearly one fourth of the cases, which can hinder reproductive outcomes.[2] In order to prevent recurrences, several measures have been suggested.[3] Advancements in technology, especially in the field of antiadhesive gels, have recently gained attention. A new cross-linked hyaluronan (NCH) gel has been used postoperatively in an attempt to decrease intra-abdominal and intrauterine adhesion formation. Two recent randomized controlled trials revealed enhanced adhesion scores either following laparoscopy[4] or hysteroscopy.[5]

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One of the commonly used adhesion re-formation prevention strategies is the placement of an intrauterine device (IUD) after hysteroscopic adhesiolysis.[6] Historically, all women with moderate-to-severe IUAs routinely have received a Lippes loop IUD after hysteroscopic adhesiolysis in our clinic.

Therefore, we hypothesized that NCH alone or in combination with an IUD may provide better adhesion prevention compared to IUD alone. Our primary objective was to compare the adhesion scores according to American Fertility Society (AFS) adhesion scoring system[7]. (**Figure 1**) at the time of the second-look hysteroscopy after the initial hysteroscopic adhesiolysis in three groups which were IUD alone, NCH alone, and combination of NCH with IUD. Our secondary objectives were to compare endometrial thickness and in vitro fertilization (IVF) outcomes in the same groups.

MATERIALS AND METHODS

This prospective study had a quasi-randomized, open-labeled design, and was conducted at our clinic between January 2015 and March 2018. The Ethics Committee approved the study protocol (99950669/256) and all participants were required to provide a signed informed consent. Participants with moderate-to-severe adhesions were consecutively assigned to IUD only, NCH only, or NCH+IUD groups at the end of the initial hysteroscopic adhesiolysis. All hysteroscopy procedures were performed by the investigator (R.P.). Inclusion criteria were 1) women aged 18 to 40 years, 2) moderate-to-severe intrauterine adhesion (AFS score ≥ 5), 3) no previous history of adhesiolysis, 4) a signed written consent prior to the initial hysteroscopy, 5) consent to have a second-look hysteroscopy, and 6) desired future fertility. Exclusion criteria were 1) minimal adhesion (AFS score < 5), 2) previous hysteroscopic adhesiolysis, 3) known or suspected intolerance or hypersensitivity to the hyaluronan gel or its derivatives or IUD, 4) genital tract malformations, and 5) acute infection. Endometrial thickness was measured using transvaginal ultrasonography (Voluson 730 Pro, GE Medical GmbH, Austria) in all women both before and after hysteroscopic interventions.

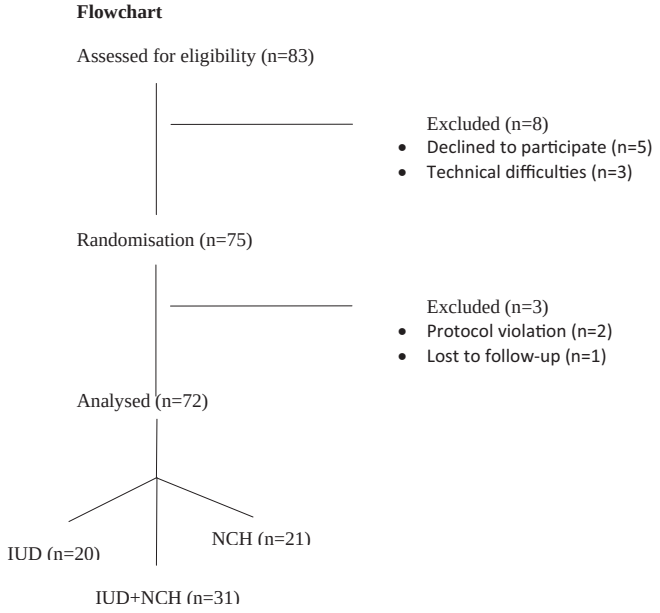

Figure 1. The American Fertility Society classification of intrauterine adhesions, 1988.[7]

Surgical Procedure

Uterine cavity was assessed using AFS adhesion scoring system (**Figure 1**) at the beginning of the procedure. A 5-F rigid hysteroscope that was equipped with hysteroscopic scissors (Karl Storz GmbH, Tuttlingen, Germany) was introduced into the uterine cavity under direct visualization. Normal saline was used as the distention medium. The adhesiolysis was initiated inferiorly and carried cephalad to the fundus using sharp dissection with the hysteroscopic scissors until the uterine cavity was normalized.

NCH Gel and/or IUD Application

At the end of the hysteroscopy procedure, 5 mL of the NCH gel (MateRegen gel, BioRegen Biomedical Ltd Inc., Changzhou, China) was injected into the uterine cavity through a 15-cm sterile delivery cannula in women assigned to the NCH gel groups. A Lippes loop IUD was inserted into the uterine cavity using a carrier cannula under transabdominal ultrasound guidance in women assigned to the IUD groups. In the NCH+IUD group, following the placement of the IUD, the NCH gel was injected into the cavity through its delivery cannula.

Followup

In all women, hormone therapy was initiated on the day of the operation, which consisted of estradiol valerate at a dose of 6 mg daily for 21 days, with the addition of medroxyprogesterone acetate at a dose of 10 mg daily for the last 7 days of estrogen therapy. After the withdrawal bleeding, hormone therapy was repeated for another cycle. Eight to 12 weeks after the initial surgery, women underwent a second-look hysteroscopy to determine the

reoccurrence of IUAs. After the assessment of the adhesion score, adhesiolysis was also carried out with hysteroscopic scissors if necessary. In women who received an IUD, a 5-F hysteroscope was inserted under direct visualization with guidance of IUD loops, and adhesiolysis was carried out beginning from the adjacent areas of the IUD.

In vitro fertilization (IVF) treatment was offered to those who were unable to conceive despite unprotective intercourse for 6 months. All women who proceeded with IVF received one to two blastocysts in a fresh cycle managed with antagonist protocol. Frozen-thaw embryo transfers, preimplantation genetic screening cycles, males with azoospermia, and cases with diminished ovarian reserve were excluded from the final data.

Statistical Analysis

Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, Illinois, USA). The normal distribution of continuous variables was determined by Kolmogorov Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Unless specified otherwise, continuous data were described as mean ± SD for normally distributed data, and median (minimum–maximum value) for skewed distributions. Categorical data were described as number of cases (%). One-way ANOVA was used to compare more than two groups for normally distributed data, and Kruskal Wallis test was applied for comparisons of the skewed data. Post-hoc analyses were performed using the least significant difference (LSD) or Conover nonparametric multiple comparison tests. Paired groups were analyzed by Wilcoxon Signed-Ranks test. A box plot graph was used for variables that were not normally distributed. Nominal data were analyzed by Pearson's χ^2 or Fisher's exact test, where applicable. A P value less than .05 was considered statistically significant.

RESULTS

Between January 2015 and March 2018, a total of 83 women were initially recruited. Among them, 5 women

Table 1.
Demographic Data and Basal Findings of the Groups

	IUD (n:20)	IUD+NCH (n:31)	NCH (n:21)	*P*
Age*	31.75 ± 4.80	32.19 ± 5.13	31.05 ± 4.72	NS
Gravida (mean ± SD)	1.1 ± 0.8	1.7 ± 0.9	1.3 ± 0.8	NS
Live births†, n (%)	1 (5.0)	2 (6.5)	3 (14.3)	NS
BMI‡ (median, min–max)	25 (19–31)	26 (19–32)	26 (8–31)	NS
Abortions‡ (median, min–max)	1 (0–3)	1 (0–4)	1 (0–3)	NS
Amenorrhea†, n (%)	11 (55.0)	17 (54.8)	13 (61.9)	NS
Oligomenorrhea†, n (%)	6 (30.0)	12 (38.7)	8 (38.1)	NS
Previous D/C, n (%)	15 (75)	24 (77)	18 (85)	NS
Mean D/C number‡ (median, min–max)	1 (0–2)	1 (0–4)	1 (0–3)	NS
Infection†, n (%)	2 (10.0)	3 (9.7)	2 (9.5)	NS
End Echo in mm (before)‡ (median, min–max)	4 (3–5)	3.5 (3–6)	4 (3–6)	NS
AFS score (before)‡ (median, min–max)	8 (5–12)[b]	8 (5–12)	8 (5–12)[b]	**.044**

AFS, American Fertility Society; BMI, Body mass index; D/C, Dilatation and Curettage; IUD, Intra uterine device; NCH, Cross linked hyaluronan; NS, Not significant.

Data are expressed as mean ± standard deviation or median (minimum–maximum) for continuous variables and number (percentage) for categorical variables.

*One-way Anova test.

†Chi-square; least significant difference (LSD) or conover-Inman test were performed for the binary comparisons among the groups and the *P* value was set at .05.

‡Kruskal wallis test.

Significant differences were found between (**a**) HS RIA vs HS ACP RIA, (**b**) HS RIA vs HS ACP, and (**c**) HS ACP RIA vs HSP ACP.

subsequently declined participation, and 3 cases were excluded due to technical difficulties (inability to reach the endometrial cavity) with the NCH gel or IUD insertion. Due to the protocol violation (n = 2) and loss of followup (n = 1), 72 women were left in the data analysis. Twenty women were in group I (IUD alone), 31 in group II (IUD+NCH) and 21 in group III (NCH alone). The baseline characteristics including age, gravidity, live births, and Body Mass Index (BMI) did not differ between the three groups. More than half of all women experienced amenorrhea before surgery. Majority of the women in all three groups had a history of at least one D/C. Initial endometrial thickness measurements and median AFS scores of the groups were comparable. Baseline data are shown in **Table 1**.

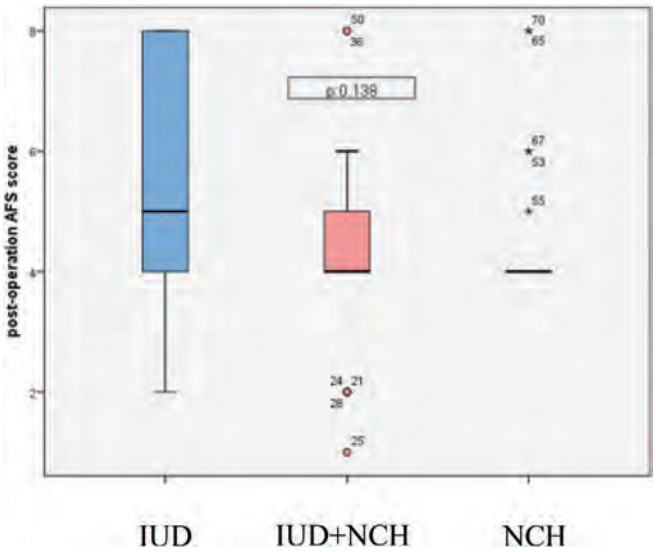

Figure 2. American Fertility Society scores following second hysteroscopy of the groups.

The mean interval between the initial and second surgery was 9 weeks in all groups. Endometrial thickness were significantly higher in group II and III than group I ($P <$ .001) prior to the second-look hysteroscopy. The AFS scores of all groups were comparable at the time of the second hysteroscopy. All groups revealed enhanced but comparable adhesion scores (P = .1) (**Figure 2**). Outcomes following the second hysteroscopy are shown in **Table 2**. However, all three intervention groups revealed significantly enhanced endometrial thickness values and AFS scores after the initial hysteroscopy ($P <$ .01) (**Table 3**) (**Figure 3**). IVF treatment was offered to those who failed to conceive within a year following the second hysteroscopy. A total of 41 women received IVF treatment in our clinic. Of those, 4 cases were excluded due to cycle cancellation and 37 were included in the analysis. Ongoing pregnancy rates were 27% (3/11), 40% (6/15), and 36% (4/11) in IUD, IUD+NCH, and NCH groups, respectively. However, the differences between the groups were not statistically significant.

DISCUSSION

In our study, all three interventions were of similar efficacy in the prevention of adhesion reformation after the hysteroscopic adhesiolysis for moderate to severe IUAs. However, better endometrial thickness values were ob-

Table 2.
Main Outcomes and ART Results of the Study Groups

	IUD (n:20)	IUD+NCH (n:31)	NCH (n:21)	*P*
Interval (weeks)*	9 (8–12)	9 (9–12)	9 (9–12)	NS
End. Echo in mm (after)*	5 (3–8)[a,b]	7.5 (4–9)[a]	6.5 (3–8)[b]	**<.001**
AFS score (after)*	5 (2–8)	4 (1–8)	4 (4–8)	NS
ART admissions (IVF/ICSI)[t]	11/20	15/31	11/21	NS
Positive hCG[†]	4/11 (36%)	6/15 (40%)	5/11 (45%)	NS
Ongoing pregnancy[†]	3/11 (27%)	6/15 (40%)	4/11 (36%)	NS

AFS, American Fertility Society; ART, Assisted Reproductive Technics; hCG, Human chorionic gonadotropin; ICSI, Intracytoplasmic sperm injection; IUD, Intra-uterine device; IVF, Invitro fertilization; NCH, New cross linked hyaluronan; NS, Not significant.

Data are expressed as median (minimum–maximum) for continuous variables and number (percentage) for categorical variables.

*Kruskal wallis test.

[†]Chi-square; least significant difference (LSD) or conover-Inman test were performed for the binary comparisons among the groups and the *P* value was set at .05.

Significant differences were found between (**a**) HS RIA vs HS ACP RIA, (**b**) HS RIA vs HS ACP, and (**c**) HS ACP RIA vs HSP ACP.

Table 3.
Endometrial Echo Measurements and AFS Scores of the Groups

	Before	After	*P*
IUD			
Echo	4 (3–5)	5 (3–8)	**.005**
AFS score	8 (5–12)	5 (2–8)	**.001**
IUD+NCH			
Echo	3,5 (3–6)	7,5 (4–9)	**<.001**
AFS score	8 (5–12)	4 (1–8)	**<.001**
NCH			
Echo	4 (3–6)	6,5 (3–8)	**<.001**
AFS score	8 (5–12)	4 (4–8)	**<.001**

AFS, American Fertility Society; IUD, Intrauterine device; NCH, New cross linked hyaluronan.

Continuous variables are expressed as either the median (minimum–maximum) and variables were compared with an Wilcoxon Signed-Ranks test.

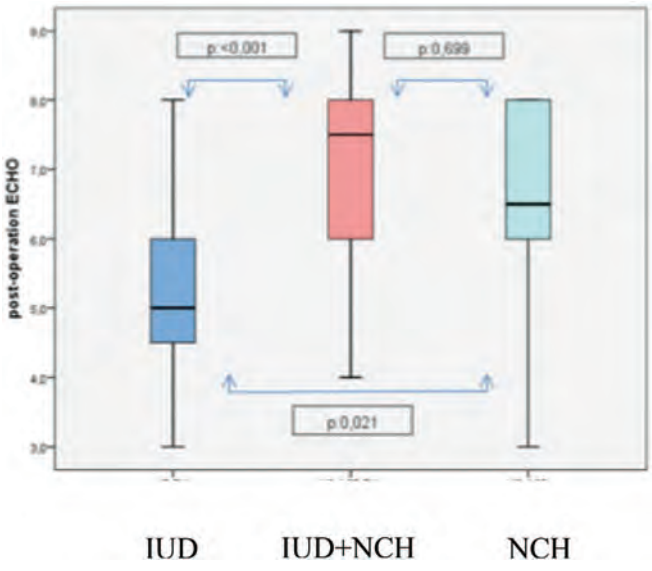

Figure 3. Endometrial thickness measurements following second hysteroscopy of the groups.

served in those who received NCH gel either alone or in combination with Lippes loop IUD.

The rate of IUA reformation after surgery remains as high as up to 24%.[2] To date, many interventions have been suggested to prevent recurrences including early second look, barrier methods such as IUDs, and hormonal therapy.[3,6,8] We have previously documented the efficacy of IUD-guided adhesiolysis in a randomized controlled trial with favorable live birth rates.[6] Particularly, Lippes loop IUD appears to enlarge the cavity most effectively and creates bits of healthy endometrium, which helps with the adhesiolysis. Moreover, additional studies also showed favorable reproductive outcomes with Lippes IUD use.[10,11] A recent American Association of Gynecologic Laparoscopists/European Society of Gynecologic Endoscopy (AAGL/ESGE) practice guideline commented in favor of Lippes loop IUD for secondary prevention.[12] In our practice, with its peculiar trapezoidal shape, the Lippes loop has been the method of choice for a long while, albeit it is no longer available in the global market.

In the last decade, antiadhesive gels mostly derived from hyaluronon have been adopted in gynecology practice to prevent both intraperitoneal and intrauterine adhesions.[13–15] Although it has distinctive functions such as reducing inflammation and improving peritoneal re-epithelialization, hyaluranon may not be suitable for endometrial surfaces due to short half-life.[16] To overcome this shortcoming, crosslinking modification has been adopted to improve in vivo persistence by increasing material viscosity and delaying degradation.[17] To date, several randomized controlled trials (RCTs) revealed promising results both in primary and secondary prevention of IUAs when compared to patients treated with hysteroscopic surgery alone.[18] Recently, a large multicenter RCT demonstrated that NCH gel application following D/C has significantly reduced adhesion reformation when compared to D/C alone.[5] In our study, mild IUAs were excluded as all cases were moderate or severe and most of them had at least one D/C procedure. This may explain our failure to find a significant decline in AFS scores in women who received the NCH gel.

Favorable results with NCH either alone or along with IUD in the literature could be attributed to optimal mechanical distention of uterine walls and/or facilitation of the biologic processes to restore the functioning of the endometrium. A recent AAGL/ESGE guideline recommended semisolid barriers, particularly auto-cross-linked hyaluranon to reduce adhesion recurrence.[13]

The differences in ongoing pregnancy rates following IVF were not significantly different in our study. Thus, all interventions seem to have similar effects on the endometrium in women who required fertility treatments. However, further studies are needed to determine whether NCH application further enhances endometrial receptivity.

The limitations of our study include a quasi-randomized design. Moreover, we lack spontaneous pregnancy rates in women who did not undergo IVF. On the other hand, a

single surgeon (R.P.) performed all hysteroscopies and scorings. Hence, reproductive outcomes were provided from a single center, which may minimize the intercenter variability.

To conclude, all interventions are of similar efficacy in the prevention of adhesion reformation after hysteroscopic adhesiolysis for moderate to severe IUAs. Despite the fact that the only outcome that improved significantly was endometrial thickness in women who received the NCH gel, further studies are needed to assess efficacy of the NCH gel in prevention of intrauterine adhesion reformation.

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GENERAL GYNECOLOGY

Cross-linked hyaluronan gel to improve pregnancy rate of women patients with moderate to severe intrauterine adhesion treated with IVF: a randomized controlled trial

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Abstract

Purpose To evaluate whether the cross-linked hyaluronan (cHA) gel can improve the clinical pregnancy rate of patients with moderate to severe intrauterine adhesion (IUA) who underwent operative hysteroscopy followed by embryo transfer.

Methods Women with moderate to severe IUA desiring to undergo embryo transfer were recruited in this randomized controlled trial. The patients were randomized on the day of receiving hysteroscopy. The control group received standard hysteroscopy, while cHA gel was applied to the treatment group at the end of hysteroscopy and 5–7 days after operation. All patients were expected to undergo in vitro fertilization (IVF)/intracytoplasmic sperm injection and frozen-thawed embryo transfer (FET).

Results A total of 306 patients were enrolled in this study, of which 202 were assigned to the treatment group and 104 to the control group. Both the clinical pregnancy rate (26.3% [49/186] vs. 15.3% [13/85], $P=0.045$), the implantation rate (17.7% [57/322] vs. 9.8% [15/153], $P=0.025$), and the endometrial thickness on the day of embryo transfer (7.97 ± 1.37 vs. 7.50 ± 0.60 mm, $P<0.001$) were significantly higher in the treatment group compared to the control group. In addition, histological assessment of the paired endometrial tissues collected before and after operation revealed a relatively higher number of tubular glands after operation (15.1 ± 13.2 vs. 28.8 ± 30.4, $P=0.166$).

Conclusions To conclude, the application of cHA gel in patients with moderate to severe IUA during hysteroscopy can improve the quality of endometrium and uterine receptivity and consequently enhance the clinical pregnancy rate after IVF/CSI and FET.

Keywords Asherman syndrome · Cross-linked hyaluronan gel · Embryo transfer · Hysteroscopy · Intrauterine adhesion · Uterine receptivity

Introduction

Intrauterine adhesions (IUAs), first described by Fritsch H in 1894 [1], are the fibrous structure that is formed in the uterine cavity as a result of endometrial trauma caused mainly by dilatation and curettage for miscarriage or induced abortion [2]. Severe IUA can lead to menstrual disturbances, pelvic pain, and even complete obliteration of the uterine cavity, which could affect the reproductive function in women [3]. Hysteroscopy currently remains the standard of care for IUA diagnosis and treatment. This minimally invasive technique allows the direct visualization of the uterine cavity and adhesiolysis mechanically. Nonetheless, it has been reported that a high rate of adhesion reformation occurs after operation, especially for patients with severe IUA [4, 5]. Repeated

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surgery several times is generally required to achieve a normalized anatomy for implantation. Thus, the key to a successful surgery is to prevent the reformation of adhesions after operation.

Anti-adhesion therapies such as intrauterine device or balloon, hormonal treatments, and barrier gels have been claimed to improve the adhesion conditions after operative hysteroscopy [6]. Hyaluronan is a water-soluble glycosaminoglycan with viscoelastic nature that can physically support the endometrial lining and prevent adhesion reformation. Its high biocompatibility makes it an ideal candidate of biomaterial used to generate barrier gel. There is no safety concern with its use in human and it is even used for the preservation of fertilized eggs. However, hyaluronan gel is rapidly degraded in the human body. To circumvent this issue, cross-linked hyaluronan gel (cHA) has been invented to prolong the half-life of the gel. Through the auto cross-linking technology, linear hyaluronan molecules are activated and modified into a three-dimensional web-like structure, which greatly enhances its stability. Previous studies had demonstrated the efficacy and feasibility of cHA gel in animals [7, 8], but there is a lack of large scale, systematically designed clinical trial to prove the clinical performance, in particular, the improvement in clinical pregnancy rate, of cHA gel in human.

In the present study, we aimed to examine the efficacy of a new cHA gel-MateRegen® gel in preventing adhesion reformation and facilitate the success rate of embryo transfer in patients with moderate to severe IUAs.

Materials and methods

Study design

This is a single-center prospective randomized controlled trial. The study protocol has been approved by the Ethics Committee of the Ninth People's Hospital of Shanghai Jiao Tong University School of Medicine (reference no.: [2014]#31), and all the patients provided written informed consent prior to entry into this study.

Study population

The study was conducted at the Department of Assisted Reproduction of the Ninth People's Hospital of Shanghai Jiao Tong University School of Medicine. A total of 306 patients with moderate to severe IUA were recruited from January 2016 to May 2017 (Supplementary Figure 1). The inclusion criteria included: (1) diagnosed as moderate to severe IUA (score ≥ 5) according to a classification system recommended by the American Fertility Society (AFS; 1988 version); (2) infertility for at least 1 year; (3) expected to undergo IVF/ICSI and FET; and (4) had at least one good quality embryo left. Patients with uterine malformations, endometrial diseases, endometriosis, and adenomyosis were excluded. The enrolled patients were randomized (2:1) on the day of receiving hysteroscopy, in which 202 were assigned to the treatment group and 104 to the control group. An administrative staff generated the random number list using SPSS and provided the treatment allocation to the physician in a sealed envelope.

Intervention

The control group received standard hysteroscopy, while cHA gel (MateRegen® gel; BioRegen Biomedical Ltd., Inc., Changzhou, China) was applied to the treatment group during hysteroscopy and 5–7 days after operation. Detailed workflow of cHA gel application is shown in Supplementary Figure 2. The MateRegen® gel used in this study is a hyaluronan gel modified through the auto cross-linking technology to enhance its stability. It has been approved by the China NMPA for clinical application.

Hysteroscopy

Hysteroscopy was performed by one of two experienced hysteroscopic surgeons using a 2.9-mm rigid hysteroscope (Karl Storz, Germany) that was equipped with hysteroscopic scissors (Karl Storz). The procedure was performed under local anesthesia with lidocaine. Saline solution was injected to distend the uterine cavity. A 300-W light source with a xenon bulb, a digital camera (Karl Storz), and a 21-inch color video monitor were used in the operation. The exploration of the uterine cavity consisted of a panoramic view of the cavity, followed by a thorough evaluation of the endometrium. The endocervical canal, uterine cavity, tubal orifices, and endometrium were inspected methodically and the findings were recorded. During hysteroscopy, both the anterior and posterior uterine walls were thoroughly examined by moving the hysteroscope along the endometrial surface to get a view parallel to the endometrial surface. In this way, any irregularity of the endometrial surface can be easily identified. Adhesions, micro polyps, and polypoid endometrium were divided or removed with the use of the hysteroscopic scissors until a normal uterine anatomy was achieved. For patients in the treatment group, the cHA gel was applied through intrauterine injection into the uterine cavity after hysteroscopic adhesiolysis.

All patients had biopsies of the endometrium for the pathological examination at the time of initial hysteroscopy. All hysteroscopies were performed in the follicular phase and images were recorded in digital format. Adhesion score was also assessed according to the AFS classification.

After hysteroscopy, all patients received 150 mg tosufloxacin tosilate (Zhuhai Pharma, Guangdong, China) tid orally for 3 days.

Embryo transfer

Embryo transfer was performed 2 months after hysteroscopy. Embryo and endometrial synchronization in cryopreserved embryo transfer cycles were performed as described by Kuang et al. [9, 10].

In this study, hormone replacement treatment was used for endometrial preparation. Oral ethinyl estradiol (25 mg; Shanghai Xinyi Pharma, Shanghai, China) tid or two red femoston tablets (Solvay Pharma, Belgium; each tablet contains 2 mg E2) bid was administered starting on day 3. For patients with thin endometrial lining, a white femoston tablet or a tadalafil tablet (Eli Lilly, Indiana, USA) was administered per vaginum as prescribed by an experienced gynecologist. Once the endometrial lining thickness was > 6.5 mm, the following medications were started: two yellow femoston tablets (each tablet contains 2 mg E2 and 10 mg dydrogesterone) bid and vaginal progesterone soft capsules (Laboratoires Besins International, France; 200 mg) bid.

The timing of embryo warming and transfer was determined on the third day after femoston administration. The maximum number of transferred embryos was two per patient. At day 14 after embryo transfer, a positive β-hCG test was performed to determine chemical pregnancy. When a pregnancy was diagnosed by means of a positive β-hCG test, femoston administration was continued and ultrasonic examination was performed 2 weeks later (Day 28) to confirm pregnancy and to determine singleton/multiple pregnancy. The progesterone supplementation was continued until 12 weeks of gestation.

It should be noted that, at our center, intervention is performed before embryo transfer in the case of patients with hydrosalpinx. Fallopian tube embolization is used when the degree of hydrosalpinx is relatively small and salpingectomy or laparoscopic tubal ligation is performed, when there is severe hydrosalpinx.

Outcome measures

Outcome measures of this study included: (1) ratio of thawed highest quality embryos = number of embryos implanted: number of thawed cycles; (2) chemical pregnancy rate = number of positive β-hCG results ÷ number of thawed cycles; (3) clinical pregnancy rate = number of pregnancy as confirmed by ultrasonic examination ÷ number of thawed cycles; (4) ectopic pregnancy rate = number of ectopic pregnancies ÷ number of clinical pregnancy; (5) singleton pregnancy rate = number of singleton pregnancies ÷ number of clinical pregnancy; (6) multiple pregnancy rate = number of multiple-fetus pregnancies ÷ number of clinical pregnancy; and (7) implantation rate = number of embryos implanted ÷ number of embryos transferred. Clinical pregnancy rate was the primary outcome measure of this study. Other outcome measures were considered as secondary outcomes.

Some patients refused implantation after hysteroscopy due to personal reasons, whereas the others had two implantations within 6 months after hysteroscopy. All implantation outcomes within 6 months after hysteroscopy were included in this study.

Histological assessment

Biopsy of the endometrium was collected from the fundus of uterus under hysteroscopy using the endometrial curette by an experienced gynecologist after intrauterine recavity. The biopsy tissue was a full thick endometrium at about 2–3 mm in diameter and was fixed in 4% paraformaldehyde. In case of severe intrauterine adhesion with an almost obliterated cavity, the suspending tissues from the fundus of uterus after recavity were collected as the biopsy of endometrium. Endometrium biopsy was done again in the treatment group during the follow-up endoscopic examination to obtain paired samples (i.e. preadministration and postadministration of cHA gel) for assessment. Eight paired samples were selected to evaluate the number of tubular glands. Endometrium biopsy samples were embedded in paraffin and sectioned at 5–7 μm thickness. For each sample, 3–5 sections were cut at the interval of 100 μm and stained with hematoxylin and eosin. The stained sections were observed under light microscopy. The morphology of the endometrium was evaluated and the number of tubular glands was counted using ImageJ program in a computer that is synchronized with the microscopic images.

Under the objective lenses' magnification of ten times, 2–3 scopes on the diagonal lines of each section were chosen for analyses. The number of tubular glands in each scope was counted and recorded, and the average number of glands in each section was calculated. The number of tubular glands in the endometrial tissue before and after the application of cHA gel was compared using paired *t* test for the paired samples collected from the eight selected patients.

Statistical analysis

Statistical analyses were performed using IBM SPSS statistical software, version 22 (IBM Corp., New York, USA). Variables were expressed as mean ± standard deviation or median (range) and compared using unpaired *t* test, Mann–Whitney test, Fisher's exact test, or Chi-squared test as appropriate. All analyses were two-tailed. Statistical significance was regarded as $P < 0.05$.

Results

Baseline characteristics

A total of 306 patients with moderate to severe IUA were recruited in this study. As shown in Supplementary Figure 1, the enrolled patients were randomly assigned to the treatment group ($n=202$) and the control group ($n=104$) on the day receiving hysteroscopy. cHA gel was applied to the treatment group during hysteroscopy and 5–7 days after operation. Detailed workflow of cHA gel application is shown in Supplementary Figure 2. No adverse reaction was observed in both groups of participants. The baseline characteristics, including age, adhesion score, infertility duration, primary infertility, previous IVF failure, history of hysteroscopy, and endometrial thickness before operation were similar among the two groups ($P>0.05$, Table 1). In addition, all the participants received the same hormonal replacement treatment for endometrial preparation. An additional treatment with white femoston tablet or tadalafil tablet was given to patients with thin endometrial lining. The number of cycles of additional treatment per the total number of thawed cycles was similar between the two groups (treatment group: 31.2% [58/186]; control group: 32.9% [28/85]).

Table 1 Baseline characteristics of the enrolled patients

Characteristics	Treatment group ($n=202$)	Control group ($n=104$)	P value[a]
Age (y)	35.9 ± 5.7	36.7 ± 4.7	0.224
Infertility duration (y)	5 (1–24)	6 (1–24)	0.113
Primary infertility (n)			0.226
Yes	27	9	
No	175	95	
Previous IVF failure (n)	2 (0–10)	2 (0–9)	0.878
History of hysteroscopy (n)	2 (0–12)	2 (0–6)	0.449
Adhesion score	8.24 ± 1.48	7.97 ± 1.41	0.109
Endometrial thickness (mm)	6.33 ± 0.97	6.31 ± 0.68	0.319

Age, adhesion score, and endometrial thickness are present as mean ± standard deviation. Other variables are present as median (range)

IVF in vitro fertilization

[a]*P* value was calculated by unpaired *t* test, Mann–Whitney test, or Chi-squared test as appropriate

Clinical outcomes of embryo transfer

As shown in Table 2, the ratio of thawed highest quality embryos (1.73 in the treatment group vs. 1.80 in the control group) was comparable in the two groups. Both the groups had a significant decrease in adhesion score after operation (treatment group: from 9.03 ± 1.15 to 2.00 ± 1.58, $P<0.001$; control group: from 8.28 ± 1.71 to 2.13 ± 1.76, $P<0.001$), with the control group showing a relatively higher incidence of readhesion (75.0% vs. 72.4%, $P=0.845$). The incidence of adhesion score ≥ 5 at follow up was also relatively higher in the control group (9.4% vs. 6.9%, $P=0.483$). The treatment group showed a relatively larger average percentage change in adhesion score (−78.0% vs. −75.6%, $P=0.536$). Significant increases in the endometrial thickness were observed in both groups (treatment group: from 6.35 ± 0.92 to 7.97 ± 1.37, $P<0.001$; control group: from 6.28 ± 0.69 to 7.50 ± 0.60, $P<0.001$). Despite there were more patients from the control group canceling embryo transfer due to the thin endometrial lining or hydrohystera ($n=19$) compared to the treatment group ($n=16$), the endometrial thickness

Table 2 Clinical circumstances and outcomes of embryo transfer

	Treatment group	Control group	P value[a]
Number of thawed cycles (n)	186	85	
Number of embryos implanted (n)	322	153	
Ratio of thawed highest quality embryos	1.73	1.80	
Adhesion score before operation[b]	9.03 ± 1.15	8.28 ± 1.71	0.089
Adhesion score at follow up[b]	2.00 ± 1.58	2.13 ± 1.76	0.906
Average change in adhesion score[b] (%)	−78.0%	−75.6%	0.536
Incidence of readhesion at follow up[b] (%)	72.4 (21/29)	75.0 (24/32)	0.845
Incidence of adhesion score ≥ 5 at follow up[b] (%)	6.9 (2/29)	9.4 (3/32)	0.483
Endometrial thickness before operation[c] (mm)	6.35 ± 0.92	6.28 ± 0.69	0.243
Endometrial thickness on the day of embryo transfer[c] (mm)	7.97 ± 1.37	7.50 ± 0.60	< 0.001
Average change in endometrial thickness[c] (%)	+27.5%	+20.7%	0.048

Adhesion score and endometrial thickness are present as mean ± standard deviation

[a] *P* value was calculated by Man–Whitney test. [b]Only 29 (treatment group) and 32 (control group) patients that were followed up for 1 month after operation were included in this analysis. [c]Only 186 (treatment group) and 85 (control group) patients that undergo embryo transfer had measured endometrial thickness available and were included in this analysis

on the day of embryo transfer was significantly higher in the treatment group ($P < 0.001$). The average percentage decrease in endometrial thickness was also significantly higher in the treatment group ($P = 0.048$).

The clinical outcomes are shown in Table 3. Outcome measures, including chemical pregnancy rate, clinical pregnancy rate, and implantation rate, were both significantly higher in the treatment group ($P < 0.05$). The two groups showed a similar singleton pregnancy rate, multiple pregnancy rate, ectopic pregnancy rate, abortion rate, and live birth rate ($P > 0.05$).

Histological assessment

Eight selected patients from the treatment group had endometrial biopsy collected during hysteroscopy and the follow-up endoscopic examination. The quality of endometrium in these paired biopsy samples was observed and compared in terms of tissue morphology and the number of tubular glands present. Our results demonstrated that a trend of increasing tubular glands was observed in the endometrium after operation (15.1 ± 13.2 vs. 28.8 ± 30.4, $P = 0.166$, Fig. 1). In addition, more fibrotic tissue was seen in the endometrium before operation compared to that after operation.

Table 3 Clinical outcomes of embryo transfer

	Treatment group	Control group	*P* value[a]
Cancel rate[b] (%)	7.9 (16/202)	18.3 (19/104)	0.007
Chemical pregnancy rate[c] (%)	34.4 (64/186)	22.4 (19/85)	0.046
Clinical pregnancy rate (%)	26.3 (49/186)	15.3 (13/85)	0.045
Ectopic pregnancy rate (%)	2.0 (1/49)	7.7 (1/13)	0.378
Singleton pregnancy rate (%)	81.6 (40/49)	76.9 (10/13)	0.703
Multiple pregnancy rate (%)	16.3 (8/49)	15.4 (2/13)	1.000
Abortion rate[d] (%)	18.4 (9/49)	38.5 (5/13)	0.147
Live birth rate (%)	81.6 (40/49)	61.5 (8/13)	0.147
Implantation rate (%)	17.7 (57/322)	9.8 (15/153)	0.025

[a]*P* value was calculated by Fisher's exact test or Chi-squared test as appropriate. [b]Embryo transfer canceled due to thin endometrial lining or hydrohystera. [c]Chemical pregnancy is defined as positive β-HCG. [d]Abortion due to ectopic pregnancy or embryo arrest (induced labor in one case of the control group due to umbilical hernia)

Discussion

IUA may cause infertility in women. Hysteroscopic adhesiolysis can improve the success rate of embryo transfer on the premise that readhesion is prevented. Hyaluronan gel has shown to be a safe and effective barrier, which can improve clinical pregnancy rate [11–13]. For cHA gel, several studies indicated that it can prevent IUA reformation after operative hysteroscopy [14, 15]. However, there is a lack of evidence that the use of cHA gel can improve the clinical outcomes of infertile women.

In this randomized controlled study, we demonstrated that the application of a new cHA gel can significantly improve the clinical outcomes of patients with moderate to severe IUA, in terms of chemical pregnancy rate, clinical pregnancy rate, singleton pregnancy rate, and implantation rate. The clinical outcomes in our study appeared to be relatively lower than those previously reported [13–15]. This is probably due to the difference in the study population. In our study, all recruited patients had infertility for at least 1 year and suffered from moderate to severe IUA. These could lead to poorer clinical outcomes. In agreement with the previous studies [14, 15], we also recognized that the use of cHA gel after hysteroscopy can significantly reduce the severity of adhesion. Although the adhesion scores at follow up were not significantly different between the two

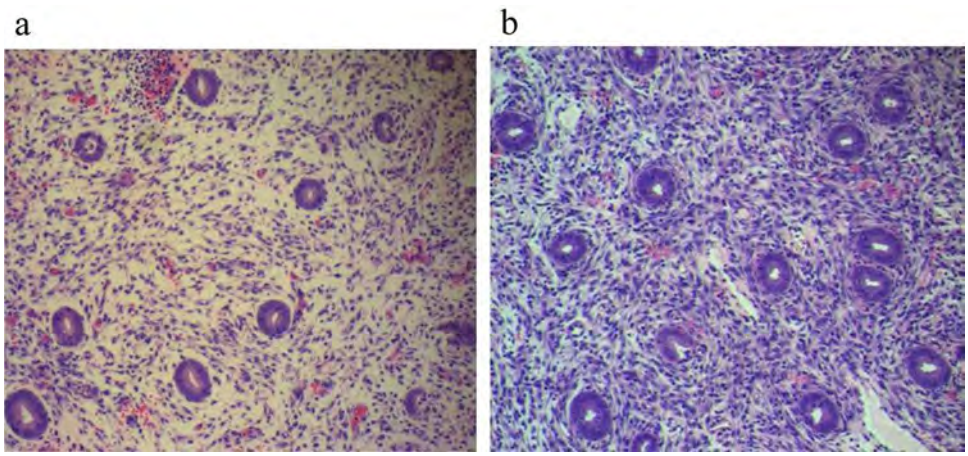

Fig. 1 Representative images of the histological assessment of the paired endometrium biopsy samples: quality of endometrium (**a**) before and (**b**) after operation

groups, the treatment group displayed a lower incidence of readhesion after operation.

To further investigate the rationale of the beneficial effect brought by cHA gel, we examined the endometrial thickness and the quality of endometrium of the recruited patients. Thin endometrial lining has been well characterized to be a major risk factor for implantation failure [16]. Zhang et al. proved that endometrial thickness can be used as a predictive factor of the endometrial receptivity in a retrospective study [17]. Theoretically, the quality of endometrium in terms of mucous gland number is also an indicator of the endometrial receptivity [18, 19]. Our results revealed that the treatment group treated with cHA gel exhibited a significantly thicker endometrial lining compared to the control group and a trend of increase in the number of glands was observed in the treatment group after operation. These supported that the cHA gel can improve the endometrial receptivity and subsequently lead to a better performance in embryo transfer.

The potential limitations of this study were listed as follow: (1) only two surgeons were assigned to perform hysteroscopy; (2) the clinicians were not blinded for the use of the gel; and (3) the small sample size of participants that finally undergo embryo transfer. These factors may affect the study quality, and thus further studies are required to validate our results.

The cHA gel used in this study-MateRegen® gel has been shown to facilitate the regeneration of nasal mucus [20]. The gel can degrade into water and completely be eliminated from the body. Thus, it is effective and safe to be used in the human body.

To the best of our knowledge, this is the first randomized controlled clinical trial reporting the use of cHA gel in a specified population, infertile woman with moderate to severe IUA, with reproductive outcomes. Adequate data such as adhesion score, endometrial thickness, and the number of glands were evaluated to support the rationale of improving endometrial receptivity with cHA gel. Together, we proved that the use of cHA gel can effectively prevent readhesion and improve the endometrial receptivity, which eventually facilitates embryo transfer in patients with moderate to severe IUA.

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Authors' contribution Shaozhen Zhang: protocol development, data collection, data analysis, manuscript writing. Jie Zhang: data collection, manuscript proofreading. Yu Tao: data collection, manuscript proofreading. Xiaoyan Mao: protocol development, data collection, data analysis, manuscript writing. Yanping Kuang: data collection, manuscript proofreading. Hongyuan Gao: data collection, manuscript proofreading. Qiuju Chen: data collection, manuscript proofreading. Renfei Cai: data collection, manuscript proofreading.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Ethics Committee of the Ninth People's Hospital of Shanghai Jiao Tong University School of Medicine; reference no.: [2014]#31) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Video Article: Synechiae treatment by the Intrauterine Bigatti Shaver (IBS)

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Abstract:

Study Objective: To confirm the validity of the Shaver technique in the treatment of postsurgical synechiae.
Design: Description of the surgical steps and prognosis according to a case report
Setting: "SELEC Sino European Life Expert Centre" of Jiao Tong University, Shanghai

Key word: Operative hysteroscopy; Asherman syndrome; Intrauterine Bigatti Shaver; Materegen gel

Casereport:

Patient: A 23 year old woman with a previous history of 3 D&C for induced abortions and two years of hypomenorrhea. 2/3D. Ultrasound in her early prolipherative phase showed a synechia inside the uterine cavity with an endometrial thickness of 3 mm. A fibrotic synechia in the fundal area of the uterine cavity was confirmed by diagnostic hysteroscopy with Campo Trophy - scope. Due to the patient's desire of pregnancy, an operative hysteroscopy with a tubal patency test was planned.

Intervention:

the operative hysteroscopy was performed with the Intrauterine Bigatti Shaver (IBS®) along with the use of scissor, Shaver blade and bipolar probe. The Shaver 24Fr optical system with SA blade was used. The rotational speed of the blade was 2100 rotatons pro minute (rpm) with a suction flow of 250 ml per minute. Initially, the 4 mm scissors, introduced through the IBS® strait operative channel, were used to cut the fibrotic synechia. Then, the Shaver SA blade removed the fibrotic tissue previously cut to restore the normal volume of the uterine cavity. The bipolar probe was used at the end of the procedure to control the bleeding. Finally, hydrotubation with methylene blue introduced inside both tubal ostia with a

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transparent silicon catheter was performed. The whole procedure lasted 6 minutes with a saline fluid deficit of approximately 300 ml. No intraoperative complications were observed, and the patient was discharged from the hospital 1 hour after the operation. The patient took Oestradiol Tablets (1mg) and Dydrogesterone Tablets (1mg) for 14 days after the operation and no antibiotic was administrated. Materegen gel by Bioregen was inserted under visual supervision inside the uterine cavity for adhesion prevention.

Main Result: At one month follow up, during the patient's early prolipherative phase, a diagnostic hysteroscopy with a Campo trophy scope was performed. The patient's periods were regular. The uterine cavity returned to its normal shape and volume with regular endometrium and without any postsurgical adhesion.

Conclusion: This case report shows that combination of the Shaver technique with gel application for postsurgical adhesion prevention should be the treatment of choice in case of synechiae or Asherman syndrome. The Shaver technique, the aim of which is not only to cut but also to remove the fibrotic tissue, combined with the gel application should improve the results of Operative hysteroscopy. The mechanical action of the Shaver without any electrosurgery is probably the reason of the promising results in this video. The Shaver optics with the bipolar probe offers a precise coagulation under direct visual control only of the vessels involved in bleeding.

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Original Article

Efficacy and safety of auto-cross-linked hyaluronic gel to prevent intrauterine adhesion after hysteroscopic electrosurgical resection: a multi-center randomized controlled trial

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Contributions: (I) Conception and design: X Tan; (II) Administrative support: None; (III) Provision of study materials or patients: H Chen, W Xiong, Y Zeng, H Du, L Ye, Y Liu, M Gong, X Dong, J Liu, L Chen, J Chen; (IV) Collection and assembly of data: H Chen, W Xiong, Y Zeng, H Du, L Ye, Y Liu, M Gong, X Dong, J Liu, L Chen, J Chen; (V) Data analysis and interpretation: H Chen, J Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: The electrothermal effect of hysteroscopic bipolar electrosurgical resection may cause damage to the endometrium, leading to intrauterine adhesion (IUA). Although some studies have demonstrated the efficacy and feasibility of auto-cross-linked hyaluronic (ACP) gel in preventing IUAs, controversy over its use continues. In this randomized controlled multi-center 2-arm parallel trial, we aimed to examine the efficacy and safety of ACP gel in preventing IUA after hysteroscopic electrosurgical resection and facilitate pregnancy in patients.

Methods: Patients from 4 centers in China were randomly assigned (1:1) to receive an intrauterine infusion of ACP gel or nothing after hysteroscopic electrosurgical resection. The randomization assignment was generated by computer and kept in a sealed envelope. A second-look hysteroscopy was performed within 3 months of the surgery.

Results: From June 2018 to May 2021, 200 patients were recruited. Ultimately, 82 patients in both groups were included in the result analysis. The baseline characteristics were comparable. The outcomes were assessed by using per-protocol analysis. The incidence of IUA in the ACP gel group was lower than that in the control group [3.66% *vs.* 10.98%, risk ratio (RR) =0.333, 95% confidence interval (CI): 0.094–1.187, P=0.072], and the planned pregnancy rate was higher than that of the control group (60.98% *vs.* 40.54%, RR =1.504, 95% CI: 0.949–2.384, P=0.071), but the difference was not statistically significant. There was no significant difference in menstruation change. Menstrual volume remained unchanged in most cases (86.59% in ACP gel group *vs.* 89.02% in the control group, RR =0.877, 95% CI: 0.877–1.109, P=0.815). Menstrual volume decreased in 10 women in the ACP gel group and 8 in the control group (12.20% *vs.* 9.76%, RR =1.250, 95% CI: 0.520–3.007, P=0.617). No adverse effects were observed after the ACP administration.

Conclusions: The present study showed that the use of ACP gel appeared to reduce both the tendency of IUA and American Fertility Society (AFS) scores and improve the subsequent pregnancy rate during hysteroscopic electrosurgical resection when treating polyps, fibroids, and uterine septum. ACP might be recommended to prevent IUA after such surgery. Further studies should be conducted with larger numbers of participants.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2100047165.

Keywords: Auto-cross-linked hyaluronic (ACP) gel; intrauterine adhesion (IUA); hysteroscopy; electrosurgical resection; randomized controlled trial

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Introduction

Intrauterine adhesions (IUAs), which were first described by Asherman in 1894 (1), are fibrous adhesive bands causing the partial or complete obliteration of the uterine cavity (2). The main symptoms of IUA include amenorrhea, oligomenorrhoea, infertility, and miscarriage (3). IUA can occur after surgical or infectious trauma to the basalis layer of the endometrium. Other etiological factors include uterine artery embolization and low estrogen status (4).

Hysteroscopy has been considered the most reliable diagnostic and therapeutic method for intrauterine diseases. It provides direct visualization of the uterine cavity and allows simultaneous surgical treatment. However, hysteroscopy may cause IUA when used as a treatment for intrauterine diseases (5). The electrothermal effect of electrosurgical resection may cause extra damage to the endometrium (6). A previous study reported that without preventive measures, new IUAs formed in 88%, 76%, and 40% of women post-operatively after septum, resection, adhesiolysis, and myomectomy, respectively (7).

Several anti-adhesion therapies exist, such as solid barriers (intrauterine contraceptive devices, stents, or balloon catheters), semi-solid barriers (hyaluronic acid or cross-linked hyaluronic gel), tissue barriers (fresh or freeze-dried amnion grafts), and hormonal treatments (4,8-12). Hyaluronic is a viscoelastic, water-soluble glycosaminoglycan that physically supports the endometrial lining and prevents adhesion formation. Its high biocompatibility makes it ideal as a barrier gel for IUA. There is no safety issue with its use in humans, and it has been used to preserve fertilized eggs. However, its fluidity and fast degradation limit its effects in treating IUA.

A cross-linking modification is an effective way to reduce the fluidity and prolong the half-life of the gel. Under this modification, linear hyaluronic molecules are activated and modified into a 3-dimensional web-like structure. The auto-cross-linked hyaluronic (ACP) gel overcomes the shortcomings of the fluidity and fast degradation *in vivo* of linear hyaluronate. ACP can stay in the uterine cavity stably and plays an effective role in isolating the uterine cavity. The product degrades in 7–14 days; however, it can play a physiological role in regulating the damaged endometrium during the critical period of endometrial repair. Several previous studies have demonstrated the efficacy and feasibility of ACP gel in preventing IUAs in animals and humans (13,14); however, controversy over its use continues. A recent randomized controlled trial (RCT) study found that there was no significant difference between the recurrence rate of IUA (31.1% *vs.* 39.8%) or the median American Fertility Society (AFS) score between the ACP gel group and the control group, and concluded that ACP gel did not seem to improve the recurrence rate of IUA after hysteroscopic adhesiolysis (15).

In the present multi-center randomized controlled trial, we aimed to examine the efficacy of ACP gel in preventing adhesion formation after hysteroscopic electrosurgical resection and in facilitating pregnancy in patients. We present the following article in accordance with the CONSORT reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4988/rc).

Methods

Trial design

This randomized controlled multi-center, 2-arm, parallel trial was approved by the Medical Ethics Committee of the West China Second University Hospital, Sichuan University (No. 2017035). The other hospitals were informed and agreed with this study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Written consent was obtained from all the included participants. Patients from the following 4 centers in China were enrolled: West China Second University Hospital, Affiliated Hospital of North Sichuan Medical College, Deyang People's Hospital, and Meishan Maternal and Child Health Hospital.

Patients who were scheduled to receive hysteroscopic bipolar electrosurgical resection were recruited. To be eligible for inclusion in this study, patients had to meet the following inclusion criteria: (I) be a female aged 18–55 years who had been diagnosed with submucosal myoma, endometrial polyp, or uterine septum; (II) provide informed consent to participate in the study and agree not to take any hormonal treatments within 3 months of the surgery; and (III) show good compliance, and be willing and able to engage in the follow-up and be observed as required.

Patients were excluded from the study if they met any of the following exclusion criteria: (I) were aged >55 years and had a body weight >100 kg; (II) were postmenopausal [follicle-stimulating hormone (FSH) >40 mIU/mL, estradiol <20 pg/mL] or pregnant; (III) had IUAs; and/or (IV) had pelvic inflammation, reproductive tract malignancy, or other severe systemic diseases.

Based on the reported rates of adhesion reformation in the literature, we estimated that the clinically reasonable reduction rate would decrease from 45% in the control group to 20% in the ACP gel group (4,16-19). Adopting a significance level of 5% and a power of 80%, the number of subjects required in each arm to demonstrate significant differences was calculated to be 79. Assuming a withdrawal rate of 20%, the total number of subjects recruited for each group was set at 100.

Randomization

The recruited patients were randomly assigned (1:1) to receive an intrauterine infusion of ACP gel (MateRegen® 3 mL, Bioregen Biomedical Co., Ltd., China) or nothing after hysteroscopic electrosurgical resection. The randomization assignment was generated by computer and kept in a sealed envelope by a statistician, who was not involved in the following treatment or follow-up of the patients. Each recruited patient was assigned an envelope consecutively by the medical staff in the ward according to the time of inclusion. The envelopes were opened by an assistant at the end of the hysteroscopy, and the surgeon used or did not use ACP gel according to the randomization. All the patients received the same observation and nursing after surgery.

Follow-up and data collection

A second-look hysteroscopy was performed within 3 months of the surgery to determine whether postoperative IUAs had occurred. The surgeons who performed the second-look hysteroscopies were not aware of whether the patient belonged to the ACP gel group or the control group. The postoperative conditions of the patients were also recorded, including menstruation and adverse reactions. Patients engaged in pregnancy planning were followed-up at least 10 months after the surgery.

Baseline data, including data on age, uterine cavity disease, history of gestation, history of uterine surgery, and previous menstruation, were collected. Detailed records were also made during the hysteroscopy, including observations on intrauterine lesions (lesion location, size and number of fibroids or polyps, and length and width of septum), the surgical wound area, the presence (or absence) of already existing IUAs, the operation time, the amount of blood loss, and the infusion (or not) of ACP gel.

Outcome measurements

The primary outcome measurement was the rate of IUA, which was confirmed by a second-look hysteroscopy within 3 months of the surgery. If IUA was confirmed, its severity and extent were scored according to the AFS classification (20). The secondary outcomes were menstrual volume change, the pregnancy rate, and adverse reactions.

Statistical analyses

The Kolmogorov-Smirnov test was used to test the data distribution. Numerical data with a skewed distribution are presented as the median [interquartile range (IQR)]. A contingency table analysis and the Chi-square test or Fisher's exact test along with risk ratios (RRs) and 95% confidence intervals (CIs) were used to compare the categorical data. A P value <0.05 in the 2-tailed tests was considered significant. All the statistical analyses were carried out using SPSS 22.0 (SPSS Corp., Chicago, IL, USA).

Results

A total of 200 patients were recruited for this study from June 2018 to May 2021. The patients were randomly divided into 2 groups with 100 in the ACP gel group and 100 in the control group. In total, 33 patients (17 in the ACP gel group and 16 in the control group) dropped out mainly due to the coronavirus disease 2019 (COVID-19) pandemic, which prevented the patients from undergoing a second-look hysteroscopy. Additionally, 3 patients were excluded, 1 of whom was postmenopausal and 2 of whom were treated with intrauterine balloons intraoperatively (1 in the ACP gel group and 1 in the control group). A flow chart of selecting patients in the trial is provided in *Figure 1*. Ultimately, the data of 82 patients in the ACP gel group and 82 patients in the control group were included in the analysis.

The baseline characteristic data, including age, weight, pregnancy rate, parity, surgical blood loss and operation time, were tested as skewed distribution data

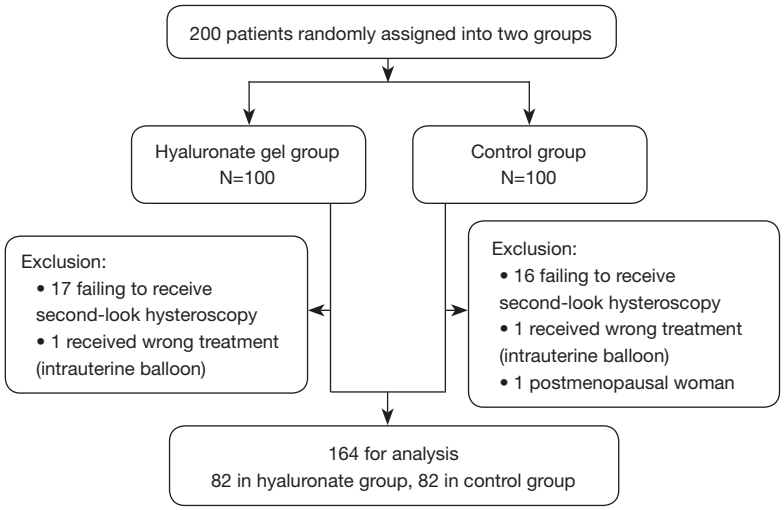

Figure 1 Flow chart of selecting patients in the trial.

Table 1 Baseline characteristic between the ACP gel group and the control group

Characteristics	ACP gel group (n=82)	Control group (n=82)
Age (years)	31 [7]	33 [12]
Weight (kg)	55 [6]	53 [10]
Gravidity	1 [2]	2 [3]
Parity	1 [1]	1 [1]
Previous uterine surgery	39 (47.56)	48 (58.54)
Uterine cavity disease		
Uterine myoma	9 (10.98)	16 (19.51)
Uterine septum	5 (6.10)	3 (3.66)
Endometrial polyp	64 (78.05)	57 (69.51)
Uterine myoma + polyp	3 (3.66)	6 (7.32)
Uterine septum + polyp	1 (1.22)	0
Wound area		
<1/3	45 (54.88)	40 (48.78)
1/3–2/3	31 (37.80)	39 (47.56)
>2/3	6 (7.32)	3 (3.66)
Previous IUA	0	0
Blood loss in surgery (mL)	5 [5]	5 [5]
Surgery time (min)	20 [10]	20 [15]

Data are shown as median [IQR] or N (%). ACP gel, auto-crossed-linked hyaluronic gel; IUA, intrauterine adhesion.

by Kolmogorov–Smirnov test, and thus represented as median (IQR) (*Table 1*). The baseline characteristics were comparable between groups. In total, there were 25 uterine myomas, 8 uterine septum, 121 endometrial polyps, 9 uterine myomas + polyps, and 1 uterine septum + polyps. None of the patients had previously been diagnosed with IUA. No adverse effects such as allergy, pain and fever were observed after the administration of the ACP gel.

The hysteroscopic and menstrual outcomes are listed in *Table 2*. The outcomes were assessed by using per-protocol analysis. Postoperative IUAs were found in 12 patients, of whom 3 were in the ACP gel group and 9 were in the control group. The incidence of IUA in the ACP gel group was lower than that in the control group, but the difference was not statistically significant (3.66% *vs.* 10.98%, RR =0.333, 95% CI: 0.094–1.187, P=0.072). All 3 cases of adhesion in the ACP gel group were mild (AFS scores 2, 2, and 3). In the control group, 2 cases of IUA were moderate (with AFS scores of 5 and 6), and the other 7 cases were mild (all with AFS scores of 2). There was no significant difference in menstruation change between the ACP gel group and the control group after hysteroscopic surgery. Menstrual volume remained unchanged in most cases (86.59% in ACP gel group *vs.* 89.02% in the control group, RR =0.877, 95% CI: 0.877–1.109, P=0.815). Menstrual volume decreased in 10 women in the ACP gel group and 8 in the control group (12.20% *vs.* 9.76%, RR =1.250, 95% CI: 0.520–3.007, P=0.617). In the control group, 1 patient

Table 2 Hysteroscopic and menstrual outcomes between the ACP gel group and the control group

Characteristics	ACP gel group (n=82), n (%)	Control group (n=82), n (%)	Risk ratio (95% CI)	P value
IUA	3 (3.66)	9 (10.98)	0.333 (0.094–1.187)	0.072
Menstrual volume change				
Less than before	10 (12.20)	8 (9.76)	1.250 (0.520–3.007)	0.617
Same as before	71 (86.59)	72 (89.02)	0.877 (0.877–1.109)	0.815
More than before	0	1 (1.22)		0.316
Amenorrhea	1 (1.22)	1 (1.22)	1.000 (0.064–15.719)	1.000

ACP gel, auto-crossed-linked hyaluronic gel; IUA, intrauterine adhesion; CI, confidence interval.

Table 3 Planned pregnancy outcomes between the ACP gel group and the control group

Characteristics	ACP gel group (n=41), n (%)	Control group (n=37), n (%)	Risk ratio (95% CI)	P value
Term delivery	15 (36.59)	9 (24.32)	1.504 (0.749–3.019)	0.241
Vaginal birth	7 (17.07)	5 (13.51)	1.263 (0.439–3.640)	0.663
Cesarean section	8 (19.51)	4 (10.81)	1.805 (0.592–5.504)	0.288
Preterm delivery	4 (9.76)	0		0.051
Spontaneous abortion	3 (7.32)	4 (10.81)	0.677 (0.162–2.827)	0.590
During pregnancy	3 (7.32)	2 (5.41)	1.354 (0.239–7.659)	0.731
Total pregnancy	25 (60.98)	15 (40.54)	1.504 (0.949–2.384)	0.071

ACP gel, auto-crossed-linked hyaluronic gel; CI, confidence interval.

had increased menstrual volume. After the surgery, 1 patient in each group had amenorrhea.

The pregnancy outcomes are listed in *Table 3*. In total, 78 patients were planning to fall pregnant (41 in the ACP gel group and 37 in the control group). The patients were followed-up for 9–40 months (median 19.6 months). In total, 40 patients fell pregnant after surgery, 25 in the ACP gel group and 15 in the control group. Additionally, 1 patient in the control group had an unplanned pregnancy and underwent an artificial abortion. The planned pregnancy rate of the ACP gel group was higher than that of the control group, but the difference was not statistically significant (60.98% *vs.* 40.54%, RR =1.504, 95% CI: 0.949–2.384, P=0.071). In total, 24 patients delivered to term, among them 12 delivered by cesarean section. Additionally, 4 women had preterm deliveries, 5 women had not yet delivered at the end of the follow-up period, and 7 women had spontaneous miscarriages. There was no significant difference between the ACP gel group and the control group in terms of the delivery rate, preterm delivery rate, and spontaneous abortion rate. No placental adhesion or implantation during pregnancy occurred in either group.

Discussion

The present study found that the number of postoperative IUAs in the control group (9 in 82 cases, 10.98%) was 3 times that of the ACP gel group (3 in 82 cases, 3.66%), and the severity of IUAs was lower in the ACP gel group. However, there was no statistical difference between the 2 groups (P>0.05), which may be due to the low incidence of IUA during hysteroscopic resection in the present study. The incidence of IUA after hysteroscopic surgery has been reported to range from 22–32% in control groups and 10–18% in ACP gel groups (18,19). Both these rates are significantly higher than those reported in the present study. Most clinical studies in this field have shown that ACP gel reduces both the tendency of IUA and AFS scores during the hysteroscopic resection of polyps, fibroids, and uterine septum (18,19,21).

In addition, ACP gel has also been reported to reduce the recurrence of IUAs after adhesiolysis (22). A network meta-analysis published in 2017 reported that the use of ACP plus a balloon was one of the most effective methods for reducing IUA recurrence and the most effective method for reducing IUA scores (23). Another recent network

meta-analysis (9) published in 2021 found that ACP gel (with or without the insertion of a copper intrauterine device) was the most effective method for preventing the recurrence of IUA after hysteroscopic adhesiolysis. The hyaluronic acid gel and the intrauterine device methods have been ranked as the most effective methods at reducing postsurgical adhesion severity.

Excluding the patients who were not planning to fall pregnant and those lost to follow-up, the planned pregnancy rate of the ACP gel group was higher than that of the control group, but the difference was not statistically significant (P<0.05). In general, no placental implantation or adhesion were observed after hysteroscopic resection. Other studies have found similar results. Thubert *et al.* assessed the effect of ACP gel on pregnancy following the hysteroscopic removal of IUAs (24), and noted that the pregnancy rate [45.8% (11/32) *vs.* 36.7% (18/58), respectively] and the viable pregnancy rate [33.3% (8/32) *vs.* 24.5% (12/58), respectively] tended to be higher in the ACP gel group than the control group. However, the results were not statistically significant (P>0.5). The authors suggested that ACP gel should be evaluated in a randomized control trial in a larger population. Mao *et al.* found that the application of ACP gel in patients with moderate to severe IUA during hysteroscopy improved the pregnancy outcomes after *in vitro* fertilization/intracytoplasmic sperm injection and frozen-thawed embryo transfer (25). The clinical pregnancy rate [26.3% (49/186) *vs.* 15.3% (13/85)], the implantation rate [17.7% (57/322) *vs.* 9.8% (15/153)], and the endometrial thickness on the day of embryo transfer (7.97±1.37 *vs.* 7.50±0.60 mm) were significantly higher in the ACP gel group than the control group (P<0.05). A recent network meta-analysis found that of the various methods used after hysteroscopic adhesiolysis (including intrauterine balloons, amnion grafts, and intrauterine devices), the ACP gel produced the highest pregnancy rate (9).

The present study had some limitations. The incidence rate of IUA after hysteroscopic resection in the present study was lower than the rates reported in the literature; thus, studies need to be conducted with larger sample sizes in the future. Additionally, 32 (16%) patients (17 in the ACP gel group and 16 in the control group) dropped out mainly due to the COVID-19 pandemic, which prevented the patients from undergoing a second-look hysteroscopy.

To conclude, the present study showed that ACP gel appears to reduce both the tendency of IUA and the AFS scores during hysteroscopic electrosurgical resection when treating polyps, fibroids, and uterine septum. However, the results were not statistically significant. The ACP gel group tended to have a higher pregnancy rate than the control group. The incidence rate of IUA after hysteroscopic resection in the present study was lower than the rates reported in the literature; thus, studies need to be conducted with larger sample sizes in the future.

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Footnote

Reporting Checklist: The authors have completed the CONSORT reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4988/rc

Trial Protocol: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4988/tp

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4988/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4988/coif). All authors report that the research was supported by Bioregen Biomedical Co., Ltd. (Changzhou, China). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of the West China Second University Hospital, Sichuan University (No. 2017035). The other hospitals were informed and agreed with this study. Written consent was obtained from all the included participants.

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Established in 2008, BioRegen Biomedical (Changzhou) Co.,Ltd., with its original proprietary self-crosslinking technology prepared sodium hyaluronate gel, which has been protected by 44 international patents, has been widely used in gynecology, otolaryngology, ophthalmology, medical beauty and other fields in China and abroad.

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