Prevalence of intrauterine adhesions after the application of hyaluronic acid gel after dilatation and curettage in women with at least one previous curettage: short-term outcomes of a multicenter, prospective randomized controlled trial

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Objective: To examine whether intrauterine application of auto-crosslinked hyaluronic acid (ACP) gel, after dilatation and curettage (D&C), reduces the incidence of intrauterine adhesions (IUAs).
Design: Multicenter; women and assessors blinded prospective randomized trial.
Setting: University and university-affiliated teaching hospitals.
Patient(s): A total of 152 women with a miscarriage of <14 weeks with at least one previous D&C for miscarriage or termination of pregnancy.
Intervention(s): Women were randomly assigned to either D&C plus ACP gel (intervention group) or D&C alone (control group). A follow-up diagnostic hysteroscopy was scheduled 8–12 weeks after the D&C procedure.
Main Outcome Measure(s): The primary outcome was the number of women with IUAs and the secondary outcome was the severity of IUAs.
Result(s): Outcomes were available for 149 women: 77 in the intervention group and 72 in the control group. The IUAs were observed in 10 (13.0%) and 22 women (30.6%), respectively (relative risk, 0.43; 95% confidence interval 0.22–0.83). Mean adhesion score and the amount of moderate-to-severe IUAs were significantly lower in the intervention group according to the American Fertility Society (AFS) and European Society of Gynecological Endoscopy classifications systems of adhesions.

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Conclusion(s): Intrauterine application of ACP gel after D&C for miscarriage in women with at least one previous D&C seems to reduce the incidence and severity of IUAs but does not eliminate the process of adhesion formation completely. Future studies are needed to confirm our findings and to evaluate the effect of ACP gel on fertility and reproductive outcomes.
Clinical Trial Registration Number: NTR 3120. (Fertil Steril® 2017;107:1223–31. ©2017 by American Society for Reproductive Medicine.)
Key Words: Intrauterine adhesions, Asherman syndrome, miscarriage, dilatation and curettage, hyaluronic acid

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Of all clinically recognized pregnancies 15%–20% will end in a miscarriage: a pregnancy that fails to progress before 20–24 weeks of gestation (1–3). Of all women trying to conceive, 5% will experience two or more miscarriages (4). Despite the availability of alternatives, most women who had a miscarriage are treated by dilatation with blunt or suction curettage (D&C).

Intrauterine adhesions (IUAs) or synechiae were first described by Heinrich Fritsch in 1894 (5). In 1948, Joseph Asherman (6, 7) described the etiology and frequency of a syndrome defined by IUAs combined with menstrual disturbance, cyclic pelvic pain, and infertility, ever since known as the Asherman syndrome. The terms IUAs and Asherman syndrome are used interchangeably, although the syndrome requires constellation of signs and symptoms (8).

The IUAs are defined as fibrous strings at opposing walls of the uterus and/or cervix leading to partial or complete obliteration of the cavity. They are reported in 19% of women after D&C for miscarriage, with 42% being moderate to severe (9). Moderate-to-severe IUAs are related to impaired fertility (8, 10). Women with a history of one or more D&C were observed to have significantly more IUAs compared with women with no history of D&C (9).

Auto-crosslinked hyaluronic acid (ACP) gel, obtained by condensation of hyaluronic acid, is a reabsorbable agent that can be applied to the uterine cavity for the prevention of IUAs. Approximately 7 days after the application, ACP is completely reabsorbed (11). The ACP gel application in hysteroscopy for subfertility and operative hysteroscopy resulted in statistical significantly lower rates of IUAs (12, 13), whereas in other studies no reduction of IUAs were reported after operative hysteroscopy and hysteroscopic adhesiolysis (14, 15).

One previous randomized controlled trial (RCT) (16) evaluated women after they had a D&C for miscarriage by hysterosalpingography (HSG). The IUAs were detected in 1 of 10 women (10%) with at least one previous D&C. These D&C were done with the application of a reabsorbable membrane containing hyaluronic acid compared with 7 of 14 women (50%) after D&C alone. The RCTs comparing the effect of ACP gel on IUAs formation after D&C for miscarriage are lacking. The aim of this study was to evaluate the effect of ACP gel application after D&C for miscarriage in women with at least one previous D&C. The incidence and severity of IUAs assessed by hysteroscopy.

MATERIALS AND METHODS

Study Design and Participants

This multicenter RCT started in December 2011 at one university hospital and two university-affiliated hospitals and during the study the number of centers were increased to reach the anticipated sample size. Finally, eight centers, one university medical center, and seven university-affiliated teaching hospitals in the Netherlands participated in the study. The trial was registered at the Dutch Clinical Trail Registry under the number NTR 3120. The study protocol was approved by National Central Committee in Research involving Human Subjects (CCMO-NL 35693.029.10.), by the ethics committee of the Free University medical center (2011/2562011/256) and by the boards of directors of all participating hospitals.

Women attending the outpatient clinic of one of the participating hospitals and who had a miscarriage, an embryonic gestation or embryonic fetal death, an incomplete miscarriage, or retained products of conception after miscarriage were counseled and offered conservative, medical, and surgical management. Women who were planned for surgery (D&C), with at least one suction or abrasive (blunt or sharp) curettage for miscarriage or termination of pregnancy, aged $\geq$18 years with a gestational age $<$14 weeks, were eligible to participate.

An ultrasound for the confirmation of a miscarriage or retained products of conception within 7 days was required for inclusion. Women were excluded in case of previous therapeutic hysteroscopy (endometrial ablation, removal of fibroids or polyps, surgical correction of congenital uterine anomalies, or adhesiolysis), suspicion of a molar pregnancy, and severe signs of infection (sepsis). All women provided written and signed informed consent before randomization.

Randomization and Blinding

Women were randomly assigned preoperatively to D&C plus ACP gel (intervention group) or D&C alone (control group). The maximum time between randomization and surgery was 1 day. Computer-generated randomization was performed by clinical staff or local study coordinator in a 1:1 ratio with variable block size, stratified by center. The study was open label to the surgeon but the women and the hysteroscopic examiner were unaware of the allocation. The medical record or operation file did not register whether or not the ACP gel was applied.

Procedures

Women were scheduled for a D&C by suction curettage in accordance with procedural standards of the Dutch society for Obstetrics and Gynecology. The intervention was performed under general, epidural, or local anesthesia according to local protocol. Histologic analysis of the obtained tissue was performed at the discretion of the surgeon or according to local standard.

Nothing was applied to the uterine cavity in women assigned to the control group at the end of the D&C procedure, whereas the ACP gel (Hyalobarrier Gel Endo, Anika Therapeutics, Abano Terme) was applied at the end of the D&C procedure in women assigned to the intervention group. In the uterine cavity and cervical canal, one sterile syringe containing 10 mL of ACP gel was applied through a 30-cm sterile cannula.

A follow-up diagnostic hysteroscopy was scheduled 8–12 weeks after the D&C procedure during the early-to-midfollicular phase of the menstrual cycle. A pregnancy test was performed and if positive, the procedure was canceled. According to protocol, the hysteroscopic examiner was not allowed to have participated or contributed to the D&C procedure and was unaware of the assignment.

The hysteroscopy was conducted without anesthesia, using saline (NaCl 0.9%) as distension medium. The instruments and imaging used for hysteroscopy in the centers were comparable. The hysteroscopic procedures were performed by experienced endoscopic surgeons or by trainees under direct supervision. The surgeon classified the type and characteristics of intrauterine pathologies observed, reported complication related to the hysteroscopic procedure, and postoperative complications related to the D&C procedure. In case of intolerance or discomfort, women were offered a procedure under local, spinal, or general anesthesia. Removal of IUAs by hysteroscopy is advised and it is the main treatment modality when IUAs are detected (17, 18). During the entire study, hysteroscopic adhesiolysis was performed if IUAs were detected. Although adhesiolysis may have an impact on long-term outcomes, it was considered unethical not to perform adhesiolysis when IUAs were detected given the negative effect on reproductive performance (10,17–19).

Data of the participants were registered in a central web-based program by staff or local study coordinator. At study entry, we collected maternal characteristics, obstetric history, and details of the current pregnancy. Characteristics of the D&C and hysteroscopic procedure were registered postoperatively. All participants received a questionnaire to record additional treatment received, complications and adverse events related to the D&C and hysteroscopic procedure including postoperative complications, menstrual pattern, and contraceptive use.

Outcomes

The primary outcome was the rate of IUAs. Secondary, short-term outcome included the severity of IUAs. To enable evaluation of the extent and degree of IUAs, a classification system is essential. The most widely used classification systems are the American Fertility Society (AFS) classification of IUAs (20) and the European Society of Gynecological Endoscopy (ESGE) classification of IUAs version 1998 (21). The severity of IUAs was prospectively assessed according to both classification systems (Supplemental Tables 1 and 2, available online).

Complications and adverse events related to the D&C, to the hysteroscopic procedure, or to the application of ACP gel were recorded. Long-term outcomes include time to conception and the number and time to clinical pregnancy, miscarriages, and ongoing pregnancies at 1 year after the D&C procedure.

Sample Size Calculation

The sample size calculation was based on the results of the only previous RCT on this subject. The IUAs were reported in 10% of women after D&C for miscarriage and application of hyaluronic acid and in 50% of women without adhesion prevention (16). Assuming a relative reduction of 50% in IUAs after application of ACP gel (from 50% to 25%) and considering a two-sided significance level of 5%, a power of 80% and a dropout rate of 15%, we needed to enroll 150 women.

Statistical Analysis

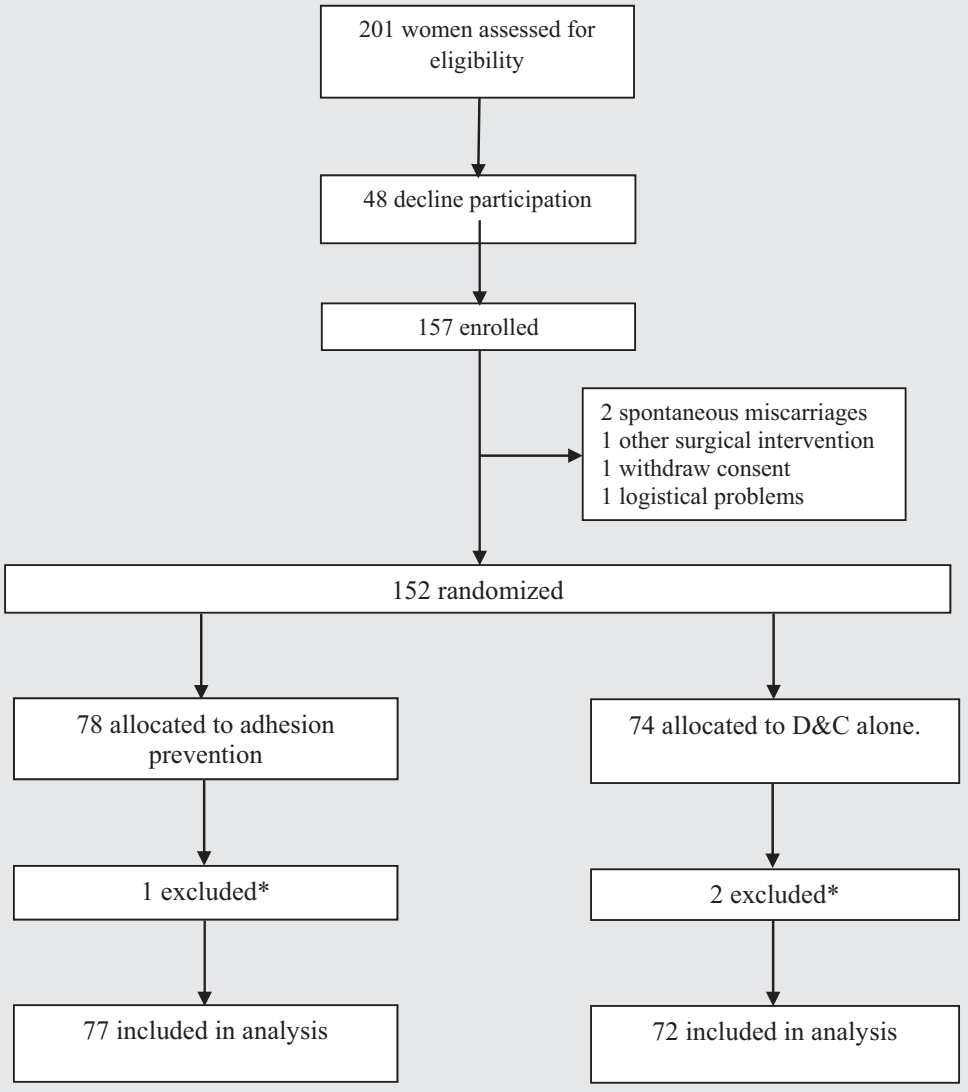
Categorical data were reported as absolute numbers and percentages. Normally distributed continuous variables were summarized as means with SDs and non-normally distributed continuous variables as medians with interquartile ranges. Primary analyses were executed using SPSS (version 20) and by independent sample *t*-test, Mann-Whitney test, χ^2 test, or Fisher's exact tests when appropriate and Stata (version 12). In addition, we carried out a per protocol analysis, including only the women who underwent a hysteroscopy. We calculated effect sizes as relative risks (RRs) with 95% confidence interval (CI) using a generalized linear model for a binary outcome and a log-link with the treatment groups as the only independent variable. When relevant we also calculated the number needed to treat to benefit and 95% CI.

To identify potential subgroups of women who may benefit the most of ACP gel application, we performed exploratory analyses. Logistic regression analyses were used to test whether the effect of the intervention differed between predefined subgroups, consisting of baseline and operation characteristics. For each subgroup variable a separate model was fitted with presence of IUAs as the dependent variable and main effects of intervention arm and subgroup variable as predictors together with their interaction. In case of a significant interaction, stratified analyses were performed estimating the RRs for the intervention group in each of the subgroups.

RESULTS

Between December 2011 and April 2015, we enrolled 152 women, randomly assigning 78 women to the intervention group and 74 to the control group. One woman in the intervention group and two women in the control group were

FIGURE 1



Flow chart of the women who participated in the Prevention of Adhesions Post Abortion (PAPA) study—a randomized controlled trial evaluating intrauterine application of auto-crosslinked hyaluronic acid gel after dilatation and curettage (D&C). *Excluded from the analysis because they did not have a previous D&C in their medical history. Not properly asked at randomization.

Hooker. Prevention of adhesions post abortion (PAPA study). Fertil Steril 2017.

excluded from analysis because they did not meet our selection criteria; they were included although they did not have a previous D&C in their history. Outcome data were available of 149 women, 77 in the intervention group and 72 in the control group (Fig. 1). The ACP gel was applied in 76 of the 77 women (98.7%) assigned to the intervention group; in one woman the ACP gel was not applied because of excessive bleeding during the D&C procedure requiring additional intrauterine measures.

Baseline characteristics of the groups were similar, although the mean gestational age at inclusion was significant lower in the intervention group compared with the control group (Table 1). None of the participants had prior uterine surgery besides cesarean section. No significant differences were observed in the details of the D&C procedure between the two groups (Table 2). Histologic analysis of the obtained tissue was performed in 29 women (37.7%) in the intervention group and in 32 women (44.4%) in the control group. A molar pregnancy was detected in two women in the control group. Signs of an infection were reported in one woman in the intervention group.

The median time interval between the D&C and hysteroscopic procedure was 10 weeks in both groups. The number of pregnant women and the number who declined to undergo a follow-up hysteroscopy were similar in both groups (Table 3). In the intervention group 60 women (77.9%) and in the control group 58 women (80.6%) underwent a follow-up diagnostic hysteroscopy. A total of 27 different endoscopic

TABLE 1

Baseline characteristics of the participants of the PAPA study.

Characteristic	Intervention group (n = 77)	Control group (n = 72)	*P* value
Age (y), mean ± SD	35.0 ± 5.0	33.9 ± 5.6	.33[a]
Age (y), range	20–44	19–44	
BMI (kg/m^2), mean (IQR)	22.7 (17.9–26.0)	24.7 (21.2–27.8)	.07[b]
White ethnic origin	69 (88.4)	58 (80.6)	.12[c]
Gravidity			.08[b]
2	20 (26.0)	22 (30.6)	
3	23 (29.9)	23 (31.9)	
≥4	34 (44.2)	27 (37.5)	
Parity			.43[b]
0	34 (44.2)	32 (44.4)	
1	25 (32.5)	32 (44.4)	
2	14 (18.2)	6 (8.3)	
≥3	4 (5.2)	2 (2.8)	
No. of previous D&C procedures			.64[c]
1	54 (70.1)	53 (73.6)	
≥2	23 (29.9)	19 (26.4)	
No. of previous miscarriages			.06[b]
0	18 (23.4)	15 (20.8)	
1	25 (32.5)	37 (51.4)	
2	20 (26.0)	15 (20.8)	
≥3	14 (18.2)	5 (6.9)	
No. of prior pregnancy terminations			.78[c]
0	54 (70.1)	49 (68.1)	
≥1	23 (29.9)	23 (31.9)	
Prior infertility treatment	10 (13.0)	6 (8.3)	.36[c]
Type of prior infertility treatment			.17[d]
Ovulation induction	2 (2.6)	3 (4.2)	
IUI	1 (1.3)	2 (2.8)	
IVF/ICSI	7 (9.1)	1 (1.4)	
Prior cesarean section	7 (9.1)	12 (16.7)	.17[c]
Gestational age (wk), mean (IQR)	8 (7–10)	9 (8–10)	.02[b]
Prior treatment			
None	46 (59.7)	42 (58.3)	.13[c]
Misoprostol	20 (26.0)	26 (36.1)	
D&C	11 (14.3)	4 (5.5)	
Type of miscarriage			
Incomplete	53 (68.8)	42 (58.3)	.18[c]
Delayed	24 (31.2)	30 (41.7)	

Note: Values are number (percentages), unless stated otherwise. BMI = body mass index; D&C = dilatation and curettage; ICSI = intracytoplasmic sperm injection; IQR = interquartile range; PAPA = prevention of adhesions post abortion.
[a] Independent samples *t*-test.
[b] Mann-Whitney test.
[c] χ^2 test.
[d] Fisher's exact test.

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surgeons performed the hysteroscopic procedures. We reviewed the charts of all participants who received a hysteroscopy and confirmed that the hysteroscopic findings were consistent with the findings reported in the digital clinical record forms completed by the endoscopic surgeons. The amount and type of congenital and acquired uterus anomalies detected at hysteroscopy did not differ between the groups (Table 3).

Prevalence and Severity of IUAs

According to intention-to-treat analysis, IUAs were observed in 10 women (13.0%) in the intervention group compared with 22 women (30.6%) in the control group (RR, 0.43; 95% CI 0.22–0.83; *P*=.013). The number needed to treat to benefit is 5.7 (95% CI 3.3–22.0).

Mean adhesion scores, assessed by the AFS scoring system was significantly lower in the intervention group compared with the control group (0.47 vs. 1.79; mean difference -1.32; 95% CI −2.00 to −0.64; *P*< .0001). The IUAs were staged as moderate or severe in 1 woman (1.3%) in the intervention group compared with 11 women (15.3%) in the control group according to the AFS classification (RR, 0.09; 95% CI 0.01–0.69; *P*=.02) and in 1 woman (1.3%) and 21 women (29.2%) according to the ESGE classification (RR, 0.05; 95% CI 0.006–0.32; *P*=.002).

Logistic regression analyses revealed no significant interactions. There was insufficient reason to believe that specific subgroups of women benefited more from the application of ACP gel than others (Supplemental Table 3, available online).

Complications and Side Effects

Complications related to the D&C procedure are reported in Table 2; no statistical significant differences were observed between the two groups. The amount of women requiring

TABLE 2

Characteristics of the D&C procedure of the participants of the PAPA study.

Characteristic	Intervention group (n = 77)	Control group (n = 72)	*P* value
Anesthetic			.07[a]
General	57 (74.0)	62 (86.1)	
Other	20 (26.0)	10 (13.8)	
Surgeon			.83[a]
Resident	42 (54.5)	38 (52.8)	
Gynecologist	35 (45.5)	34 (47.2)	
Cervix dilatation performed	59 (76.6)	60 (83.3)	.31[a]
Antibiotic administered	9 (11.7)	6 (8.3)	.51[a]
Blood loss (mL), mean (IQR)	50 (50–112.5)	50 (50–100)	.95[c]
Complications			
Excessive bleeding	3 (3.9)	1 (1.4)	.62[b]
Uterus perforation	1 (1.3)	0 (0)	1.00[b]
Cervix laceration	1 (1.3)	0 (0)	1.00[b]
Extra outpatient clinic visits	13 (16.9)	10 (13.9)	.66[b]
Postoperative infection	2 (2.6)	1 (1.4)	1.00[b]
Postoperative pain	4 (5.2)	3 (4.2)	1.00[b]
Postoperative bleeding	6 (7.8)	5 (6.9)	1.00[b]
Incomplete evacuation	2 (2.6)	1 (1.4)	1.00[b]
Histology performed	29 (37.7)	32 (44.4)	.41[b]
Molar pregnancy	0 (0)	2 (2.8)	.23[b]
Signs of infection	1 (1.3)	0 (0)	1.00[b]

Note: Values are number (percentages), unless otherwise stated. D&C = dilatation and curettage; IQR = interquartile range; PAPA = prevention of adhesions post abortion.
[a] χ^2 test.
[b] Fisher's exact test.
[c] Mann-Whitney test.

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additional outpatient visits was similar between the groups: 13 women (16.9%) in the intervention group versus 10 women (13.9%) in the control group. Two women in the intervention group and one woman in the control group underwent a second D&C procedure because of incomplete evacuation. To our knowledge no gel-related complications or adverse events were reported in the intervention group. The rate of complications related to the hysteroscopic procedure were similar in both groups (Table 3).

Per Protocol Analysis

As the number of women who did not undergo a hysteroscopy was higher than expected, we conducted additional analysis including only women who received a hysteroscopy. The primary outcome did not change significantly; IUAs were observed in 10 of the 60 women (16.7%) in the intervention group compared with 22 of 58 women (37.9%) in the control group (RR, 0.44; 95% CI 0.23–0.85; *P*=.014). The number needed to treat to benefit is 4.7 (95% CI 2.8–19.3).

Mean adhesion score remained significantly lower in the intervention group compared with the control group (2.80 vs. 4.70; mean difference −1.90; 95% CI −3.61 to −0.19; *P*=.03). According to the AFS classification system, one woman (1.7%) in the intervention group compared with 11 women (19.0%) in the control group had moderate-to-severe IUAs (RR, 0.09; 95% CI 0.01–0.66; *P*=.018) and, according to the ESGE classification system, one woman (1.7%) in the intervention group compared with 21 women (36.2%) in the control group had moderate-to-severe IUAs (RR, 0.05; 95% CI 0.01–0.33; *P*=.002).

DISCUSSION

Principal Findings

In this multicenter RCT, intrauterine application of ACP gel after conventional D&C for miscarriage in women with a history of at least one D&C, reduces the cumulative rate and severity of IUAs and is associated with a lower mean adhesion score compared with D&C alone. Less moderate-to-severe IUAs were observed according to the AFS and ESGE classification systems.

In a per protocol analysis the results did not changed; significantly less IUAs were observed in the intervention group. The severity of the IUAs and the amount of moderate-to-severe IUAs according to both classification systems and mean adhesions scores remained statistically significantly lower in the intervention group. The rate of complications were similar in both groups. Intrauterine application of ACP gel does not eliminate the process of adhesion formation completely, but reduces the intensification of IUAs.

Strengths and Weaknesses

Our study has several strengths. The Prevention of Adhesion Post Abortion (PAPA) study is the largest multicenter RCT so far comparing the immediate application of ACP gel after D&C for miscarriage with no antiadhesive treatment in women with a history of at least one previous D&C. This is a population with an increased risk of IUAs (9). Furthermore, the hysteroscopic surgeon assessing the existence and severity of IUAs and the women were blinded for the assigned treatment. The severity of IUAs was prospectively graded by experienced clinicians according to the two most accepted

TABLE 3

Details and results of the follow-up hysteroscopic procedure of the participants of the PAPA study.

Characteristic	Intervention group n = 77	Control group n = 72
No hysteroscopy	17 (23.1)	14 (19.4)
Pregnant	10 (13.0)	6 (8.3)
Declined	7 (9.1)	8 (11.1)
Hysteroscopy performed	60 (77.9)	58 (80.6)
Interval between D&C and hysteroscopy	n = 60	n = 58
Mean, wk (mean ± SD)	10 (8–12)	10 (9–12)
<12	44 (73.3)	46 (79.3)
13–16	10 (16.7)	7 (12.1)
>17	6 (10.0)	4 (6.9)
Hysteroscopic findings	n = 77	n = 72
IUAs	10 (13.0)	22 (30.6)
Other detected anomalies		
Retained products of conception	11 (14.3)	8 (11.1)
Congenital uterine anomalies	3 (3.9)	2 (2.8)
Uterus septum	1 (1.3)	2 (2.8)
Unicornis	1 (1.3)	0 (0)
Didelpis	1 (1.3)	0 (0)
Acquired anomalies (Myoma)	2 (2.6)	1 (1.4)
Complications	n = 60	n = 58
Uterus perforation	1 (1.7)	0 (0)
Bleeding	0 (0)	0 (0)
Intravasation of medium (>500 mL)	0 (0)	0 (0)
Infection	0 (0)	0 (0)
Patient discomfort	2 (3.3)	1 (1.7)
Adhesion score[a]	n = 60	n = 58
Mean (±SD)	2.8 ± 0.87	4.4 ± 2.31
Extent of IUAs according to AFS	n = 10	n = 22
Stage I (mild)	9 (90)	12 (54.5)
Stage II (moderate)	1 (10)	9 (40.9)
Stage III (severe)	0 (0)	1 (4.5)
Extent of the IUAs according to ESGE	n = 10	n = 22
Stage I, II, or IIIa (mild)	9 (90)	1 (4.5)
Stage III (moderate)	1 (10)	14 (63.6)
Stage IV, Va, or Vb (severe)	0	7 (31.8)

Note: IUAs were graded according to: American Fertility Society (AFS) or European Society of Gynecological Endoscopy (ESGE) classification system. IUA = intrauterine adhesion; PAPA = prevention of adhesions post abortion.

[a] Adhesion score is based on the cumulative scores of the classification of the American Fertility Society (AFS).

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and international-adapted classification systems. The robustness of our data was underlined by comparable outcomes in the intention-to-treat and the per protocol analyses.

Our study also has some limitations. The main weakness of the study is that blinding of the surgeon performing the D&C procedure was not possible; placebo for intrauterine application was not available. To prevent bias, the hysteroscopic examiner was not allowed to participate in the D&C procedure. Although hysteroscopy is considered the gold standard for diagnosing intrauterine pathologies (22, 23), hysteroscopy remains a subjective method for assessment of intrauterine pathologies, including IUAs, with a poor-to-moderate interobserver agreement (23–26). Unfortunately, in the current study the abnormalities encountered during the endoscopic procedures were not graded by a second observer.

The recruitment period was longer than anticipated although the number of centers were increased during the study. Although, two international-adapted classification systems for IUAs were used, none have been validated and are not linked to reproductive performance or outcome. The presence of pre-existing IUAs, experience of the surgeon, variation in practice of D&C and hysteroscopy procedure with difference in surgical techniques and instrumentation being used could have influenced the results. The mean gestational age of the intervention group was significant lower compared with the control group, which could have influenced the presented results.

In the current study we performed additional analyses that were not predefined in the study protocol. Approximately 80% of the participants underwent a follow-up hysteroscopy and the sample size was based on a 10%–15% dropout rate. A per protocol analysis, restricting to women who underwent a follow-up diagnostic hysteroscopy, confirmed the earlier outcomes, supporting the robustness of our findings. Furthermore, exploratory logistic analyses did not identify subgroups of women who may benefit the most from ACP gel application.

Finally, IUAs should be considered a surrogate indicator. Possibly more relevant are long-term fertility, reproductive outcome, and obstetric complications. In addition we will study the effect of ACP on reproductive outcomes after a longer follow-up of the included patients. However, because IUAs were treated during the hysteroscopic follow-up it can

be questioned if the differences on reproductive outcomes persist. Nevertheless, there is a relationship between the presence and especially extent of IUAs and reproductive performance (17).

The IUAs are the major long-term complication of D&C. The possible underlying mechanism of infertility due to IUAs is not well understood, but may be related to obstruction of sperm transport, impaired embryo migration, or failure of embryo implantation due to endometrial insufficiency (8, 10). A D&C is a common surgical intervention performed in daily practice and still frequently applied worldwide in women with a miscarriage.

Comparison with Other Studies

Our results are in accordance with the only previous RCT on this subject, in which women were evaluated by HSG (16). The sensitivity and specificity of hysteroscopy for detection of IUAs is higher compared with HSG (27, 28). The IUAs are thought to develop as a result of trauma to the uterine cavity, leading to adherence of the walls of the uterus in the healing process (17, 19). Adhesion formation is multifactorial with multiple predisposing and causal factors while the pathogenetic mechanism is still poorly understood.

Pregnancy is the major predisposing factor, nearly 90% of cases are pregnancy related (17, 19). The main mechanism of adhesion prevention is to avoid any event that causes damage to the endometrium. Expectative management should be considered a treatment option in women with a miscarriage; 50% will evacuate spontaneously and completely within 2 weeks (29). Medical management with misoprostol is a noninvasive alternative, which is cost-effective and as effective as D&C in achieving complete evacuation with good patient satisfaction (30). No IUAs were reported in women with a miscarriage treated by expectant or medical management (9). Earlier strategies for prevention of IUAs have included intrauterine insertion of a Foley catheter, insertion of intrauterine devices (IUDs), postoperative administration of estrogen (E), and most recently the application of reabsorbable barriers.

According to a systematic review and meta-analysis, there is a lack of evidence to conclude that any treatment is effective in preventing IUAs after hysteroscopy (31). The available data on hyaluronic acid or ACP after operative hysteroscopy are inconsistent with significant heterogeneity and a high risk of bias, making it impossible to draw definite conclusions and also the impact on reproductive outcomes have not been evaluated.

The health burden and costs associated with IUAs are unknown, but are estimated to be substantial (32). Whether application of ACP gel in women undergoing D&C for miscarriage without a previous D&C could have a favorable effect on the rate and severity of IUAs remains undetermined and could not be recommended on basis of the result of the current study. In an animal model, improved fertility was reported after the immediate application of ACP gel after intrauterine surgery likely to cause IUAs (33). The effect on long-term fertility and reproductive outcome in human is still unknown and is a reason for further research.

Conclusions and Policy Implication

Our RCT shows reduction in the incidence and severity of IUAs, lower mean adhesion scores, and less moderate-to-severe IUAs after application of ACP gel in women with a history of at least one D&C, undergoing D&C for miscarriage based on hysteroscopic assessment. This is a specific group of women with an increased risk for clinically significant adhesion. No differences were reported in terms of complications or side effects. Prevention of IUAs is essential and application of ACP gel may be considered to reduce the incidence and severity of IUAs. Future studies are needed to confirm our findings and to compare gel with and without ACP to ensure the effect of ACP on adhesion prevention. Larger studies with a longer follow-up are needed to study the effect of ACP gel application after a D&C for miscarriage on clinically relevant parameters, fertility, and reproductive outcomes.

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SUPPLEMENTAL TABLE 1

The American Fertility Society (AFS) classification of intrauterine adhesions, 1988.

Variable	Adhesion score		
Extent of cavity involved (score)	<1/3 (1)	1/3–2/3 (2)	>2/3 (4)
Type of adhesions (score)	Filmy (1)	Filmy & dense (2)	Dense (4)
Menstrual pattern (score)	Normal (0)	Hypomenorrhea (2)	Amenorrhea (4)

	Prognostic classification scores
Disease severity	
Stage I (mild)	1–4
Stage II (moderate)	5–8
Stage III (severe)	9–12

Note: Disease severity is based on cumulative score.

Hooker. Prevention of adhesions post abortion (PAPA study). Fertil Steril 2017.

SUPPLEMENTAL TABLE 2

European Society of Gynecological Endoscopy (ESGE) classification of intrauterine adhesions (1998 version).

Grade	Extent of intrauterine adhesions[a]
I	Thin or filmy adhesions easily ruptured by hysteroscope sheath alone. Cornual areas normal
II	Singular dense adhesion connecting separate parts of the uterine cavity. Visualization of both tubal ostia possible. Cannot be ruptured by hysteroscope sheath alone
IIa	Occluding adhesions only in the region of the internal cervical os.[b] Upper uterine cavity normal
III	Multiple dense adhesions connecting separate parts of the uterine cavity. Unilateral obliteration of ostial areas of the tubes
IV	Extensive dense adhesion with (partial) occlusion of the uterine cavity. Both tubal ostial areas (partially) occluded
Va	Extensive endometrial scarring and fibrosis in combination with grade I or grade II adhesions with amenorrhea or pronounced hypomenorrhea
Vb	Extensive endometrial scarring and fibrosis in combination with grade III or grade IV adhesions with amenorrhea

[a] From findings at hysteroscopy or hysterography.
[b] Only to be classified by hysteroscopy.

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SUPPLEMENTAL TABLE 3

Logistic regression analyses of the PAPA study.

Potential effect modifier	*P* value interaction with group
Parity (0 vs. ≥1)	.84
D&C procedure (1 vs. ≥2)	.53
TOP (0 vs. ≥1)	.81
Previous miscarriage (0 vs. ≥1)	.31
Previous treatment current miscarriage (none, D&C or misoprostol)	.70
Type of miscarriage (incomplete vs. delayed)	.38
Dilation (yes vs. no)	.97
Surgeon (resident vs. gynecologist)	.29

Note: D&C = dilatation and curettage; PAPA = prevention of adhesions post abortion; TOP = termination of pregnancy.

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