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;■:■–■. ©2017 by American Society for Reproductive Medicine.)
Key Words: Intrauterine adhesions, Asherman syndrome, miscarriage, dilatation and curettage, hyaluronic acid

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.