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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

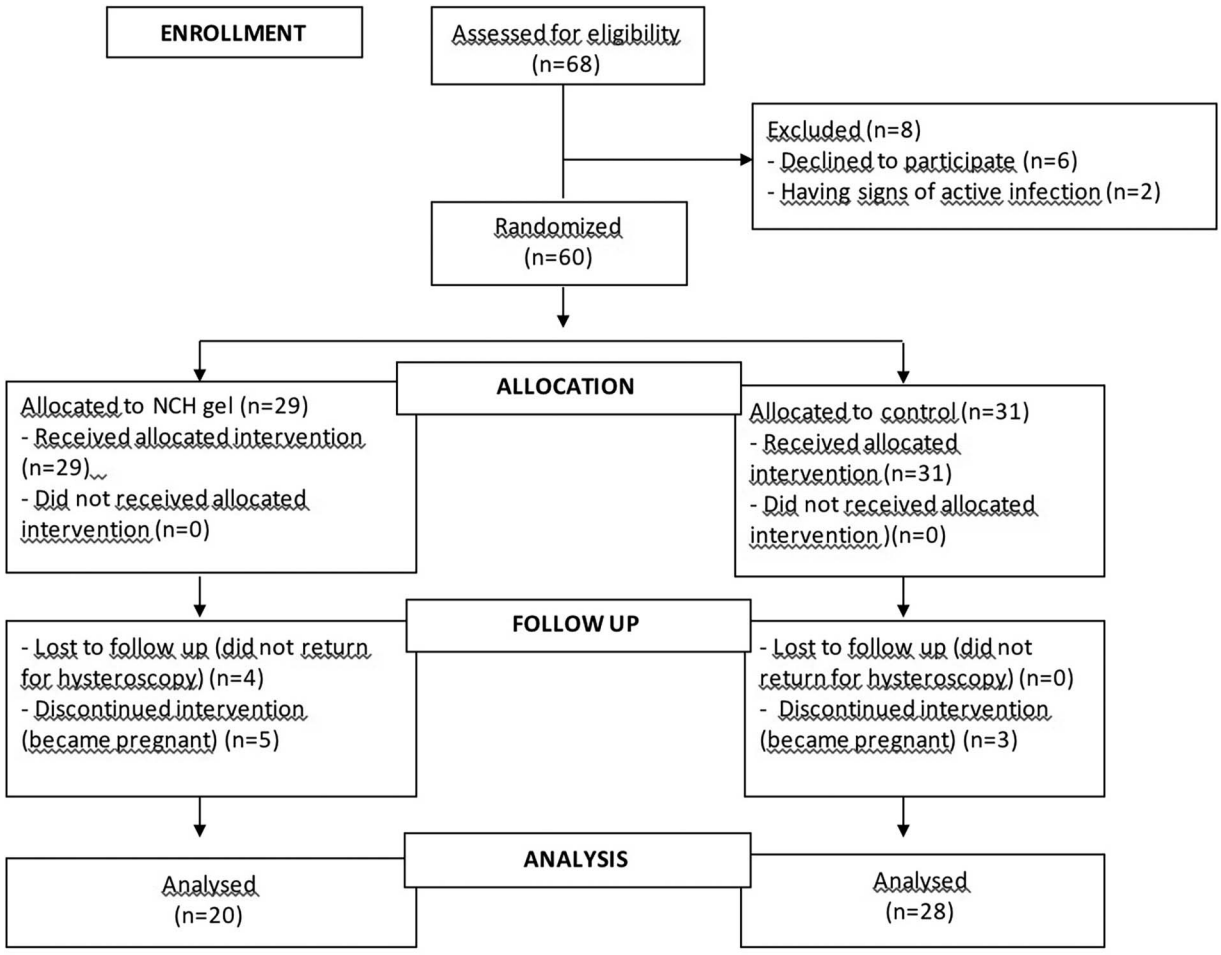

Figure 1. CONSORT flow diagram of participants.

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.

References

1. Schenker JG, Margalioth EJ. Intrauterine adhesions: an updated appraisal. *Fertil Steril.* 1982;37:593–610.

2. Schenker JG. Etiology of and therapeutic approach to synechia uteri. *Eur J Obstet Gynecol Reprod Biol.* 1996;65:109–113.

3. Dalton VK, Saunders NA, Harris LH, Williams JA, Lebovic DI. Intrauterine adhesions after manual vacuum aspiration for early pregnancy failure. *Fertil Steril.* 2006;85:1823.e1e3.

4. Yu D, Wong YM, Cheong Y, Xia E, Li TC. Asherman syndrome – one century later. *Fertil Steril.* 2008:89;759–779.

5. Valle RF and Sciarra JJ. Intrauterine adhesions: hysteroscopic diagnosis, classification, treatment, and reproductive outcome. *Am J Obstet Gynecol.* 1988;158:1459–1470.

6. AAGL practice report: practice guidelines for management of intrauterine synechiae. *J Minim Invasive Gynecol.* 2010;17:1–7.

7. Hooker AB, Lemmers M, Thurkow AL, et al. Systematic review and meta-analysis of intrauterine adhesions after miscarriage: prevalence, risk factors and long-term reproductive outcome. *Hum Reprod Update*. 2014;20:262–278.

8. Adoni A, Palti Z, Milwidsky A, Dolberg M. The incidence of intrauterine adhesions following spontaneous abortion. *Int J Fertil*. 1982;27:117.

9. Gilman AR, Dewar KM, Rhone SA. Intrauterine adhesions following miscarriage: look and learn. *J Obstet Gynaecol Can*. 2016;38:453–457.

10. Taskin O, Sadik S, Onoglu A, et al. Role of endometrial suppression on the frequency of intrauterine adhesions after resectoscopic surgery. *J Am Assoc Gynecol Laparosc*. 2000;7:351–354.

11. Guida M, Acunzo G, di Spiezio Sardo A, et al. Effectiveness of auto-crosslinked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic surgery: a prospective, randomized, controlled study. *Hum Reprod*. 2004;19:1461–1464.

12. Acunzo G, Guida M, Pellicano M, et al. Effectiveness of auto-crosslinked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic adhesiolysis: a prospective, randomized, controlled study. *Hum Reprod*. 2003;18:1918–1921.

13. Bosteels J, Weyers S, Kasius J, Broekmans FJ, Mol BW, D'Hooghe TM. Antiadhesion therapy following operative hysteroscopy for treatment of female subfertility. *Cochrane Database Syst Rev*. 2015;9:CD011110.

14. American Fertility Society. American Fertility Society classifications of adnexal adhesions, distal tubal occlusion, tubal occlusion secondary to tubal ligation, tubal pregnancies, mullerian anomalies and intrauterine adhesions. *Fertil Steril*. 1988;49:944–955.

15. Renier D, Bellato PA, Bellini D, Pavesio A, Pressato D, Borrione A. Pharmacokinetic behaviour of ACP gel, an auto-crosslinked hyaluronan derivative, after intraperitoneal administration. *Biomaterials*. 2005;26:5368–5374.

16. Huberlant S, Fernandez H, Vieille P, et al. Application of a hyaluronic acid gel after intrauterine surgery may improve spontaneous fertility: a randomized controlled trial in New Zealand White rabbits. *PLoS One*. 2015;10:e0125610.

17. Hooker AB, de Leeuw R, van de Ven PM, et al. 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. *Fertil Steril*. 2017;107:1223–1231.

18. Tsapanos VS, Stathopoulou LP, Papathanassopoulou VS, Tzingounis VA. The role of Seprafilm bioresorbable membrane in the prevention and therapy of endometrial synechiae. *J Biomed Mater Res*. 2002;63:10–14.

19. Kajanoja P, Aantaa K. Radiographic findings in cervix uteri after prostaglandin abortion induction. *Acta Obstet Gynecol Scand*. 1983;62:253–256.

20. March CM. Asherman's syndrome. *Semin Reprod Med* 2011; 29:83–94.

21. Goldenberg M, Schiff E, Achiron R, Lipitz S, Mashiach S. Managing residual trophoblastic tissue. Hysteroscopy for directing curettage. *J Reprod Med*. 1997;42:26–28.

22. Cohen SB, Kalter-Ferber A, Weisz BS, et al. Hysteroscopy may be the method of choice for management of residual trophoblastic tissue. *J Am Assoc Gynecol Laparosc*. 2001;8:199–202.

23. Capella-Allouc S, Morsad F, Rongières-Bertrand C, Taylor S, Fernandez H. Hysteroscopic treatment of severe Asherman's syndrome and subsequent fertility. *Hum Reprod*. 1999;14:1230–1233.