Hyaluronic acid gel improves pregnancy outcomes after repeated dilatation and curettage

The Post Abortion Prevention of Adhesions (PAPA) study, a multicenter prospective randomized controlled trial (RCT) from a Dutch team, studied the effect of application of autocrosslinked hyaluronic acid (ACP) gel for intrauterine adhesions (IUAs) after dilatation and curettage (D&C) for miscarriage in women who have experienced at least one previous D&C (1). The ACP gel (obtained from hyaluronic acid condensation), is a resorbable gel administrated into the uterine cavity after D&C in an attempt to reduce IUAs. In the first part of the study, all patients had a follow-up hysteroscopy 8–12 weeks after D&C when the IUAs were evaluated according to the two most accepted classifications by the American Fertility Society and the European Society of Gynecological Endoscopy. The rate of IUAs differed between the groups, as follows: 13% among the intervention group and 30.6% among the control group. The ACP gel reduced the rate of IUAs with a relative risk (RR) of 0.43. Furthermore, in the intervention group the rate of moderate-to-severe IUAs was lower than in the control group. In addition, adhesiolysis was more often performed in the follow-up hysteroscopy among control patients, which might have diluted differences between the cases and the controls regarding pregnancy and fertility outcomes, as reported in a subsequent article by the study group (2).

The relationship between IUAs and adverse reproductive outcomes is well known. The IUAs may predispose women to infertility and recurrent miscarriages. Trauma is the major cause of IUAs and individual factors, such as age, race, nutritional status, and infectious disease processes, also influence adhesion formation (3). According to a systematic review (3) IUA prevention includes good surgical technique, an early therapeutic second-look hysteroscopy, and barrier methods (such as ACP gel). The role of hormonal or antibiotic treatments remains unknown.

In addition to affecting reproduction, IUAs may cause menstrual abnormalities, dysmenorrhea, and pelvic pain. The IUAs may also obstruct the cervix, which may lead to hematometra, pain, and difficulties in obtaining endometrial samples or in entering the uterine cavity at hysteroscopy. However, clinical reproductive outcomes, such as a lower miscarriage rate, a shorter time to conception, and an improved live birth rate, are most important for the patient.

In the third part of the Dutch study, questionnaires were sent to patients 30 months after randomization. These included questions about menstruation, contraception, and pregnancies. Women in the control group tried to conceive more often and they actually did (77.6% vs. 92.2%). However, significantly more ongoing pregnancies (74.6% vs. 67.2%) were detected among the intervention group and this difference increased further when adjusted for age (2). Median time to conception leading to live birth was shorter (21.9 vs 36.1 months). Also, miscarriage rate was lower in the intervention group. The live birth rate, ectopic pregnancy, and termination of pregnancy rates were similar. Although the study was not powered to evaluate reproductive outcomes, the findings are important, demonstrating that ACP gel improves pregnancy outcomes among women with repeated D&Cs.

A recent meta-analysis (4) evaluated the efficacy of hyaluronic acid gel in preventing IUAs after different uterine operations. Researchers found seven RCTs including the aforementioned Dutch studies with a total of 952 patients. The use of hyaluronic acid gel reduced the incidence and the severity of IUAs by almost 60% (RR 0.42, 95% confidence interval 0.30–0.57) regardless of the type of surgery performed (hysteroscopy or D&C). In addition, hyaluronic acid gel improved the pregnancy rates after intrauterine operations (RR 1.94, 95% confidence interval 1.46–2.60). However, the investigators concluded that follow-up data in these studies were insufficient to evaluate the effect on postoperative pregnancy or live birth rate. Therefore, it is very important that the 42-month results of the PAPA study are published at present. I congratulate the investigators for their invaluable work. Preforming such a high-quality RCT requires a lot of work. The methodology in the study was meticulous and the drop-out rate is extremely low.

High-quality RCTs to assess the effectiveness of antiadhesion agents are still needed before these strategies may be strongly recommended for routine use to improve pregnancy outcomes in women undergoing intrauterine operations (4). In the meantime, healthcare providers should carefully evaluate available data of these agents and determine whether to support their routine, prophylactic use. We can already conclude that ACP gel should be offered to women undergoing repeated D&C. The Dutch collaboration should encourage other countries to build similar consortiums that effectively build RCT studies.

Maija Jakobsson, M.D.
Department of Obsterics and Gynecology, HUS Hyvinkää hospital, University of Helsinki, Helsinki, Finland

https://doi.org/10.1016/j.fertnstert.2020.07.004

You can discuss this article with its authors and other readers at
https://www.fertstertdialog.com/posts/30917

REFERENCES

1. Hooker AB, de Leeuw R, van de Ven PM, Bakkum EA, Thurkow AL, Vogel NEA, 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;107:1223–31.
2. Hooker AB, de Leeuw R, Twisk JWR, Brölmann HAM, Huirne JAF. Pregnancy and neonatal outcomes up to 42 months following application of hyaluronic acid gel after dilatation and curettage for miscarriage in women who have experienced at least one previous curettage; follow-up of a randomized controlled trai. Fertil Steril. 2020;114:601–9.
3. Di Spiezio Sardo A, Calagna G, Scognamiglio M, O'Donovan P, Campo R, de Wilde RL. Prevention of intrauterine post-surgical adhesions in hysteroscopy. A systematic review. Eur J Obstet Gynecol Reprod Biol 2016;203:182–92.
4. Zheng F, Xin X, He F, Liu J, Cui Y. Meta-analysis on the use of hyaluronic acid gel to prevent intrauterine adhesion after intrauterine operations. Exper Therap Med 2020;19:2672–8.