Antiadhesion barrier gels: time for evidence-informed practice in gynecologic surgery?

The Prevention of Adhesions Post Abortion (PAPA) study published by Hooker and coworkers (1) reports a decrease in the occurrence of intrauterine adhesions (IUAs) after the intrauterine application of auto-crosslinked hyaluronic acid (ACP) gel after dilation and curettage (D&C) for miscarriage in women with at least one previous D&C. The mean adhesion scores and the amount of moderate to severe IUAs were both statistically significantly lower after the application of the antiadhesion barrier gel compared with D&C alone (1). The evidence suggests, under the assumption of a prevalence of IUAs after at least one D&C of 31%, that the use of ACP gel may decrease the risk of IUAs with 57% (95% confidence interval, 17% to 78%).

The PAPA-study is the largest multicenter randomized controlled trial comparing the application of antiadhesion barrier gel after D&C for miscarriage with no antiadhesion treatment in a population at risk for IUAs. Both participants and outcome assessors were blinded to the allocated treatment. The data and the conclusions of the study are robust: sensitivity analyses according to an intention-to-treat analysis including all 152 randomized participants or a per-protocol analysis including only 118 women who underwent a follow-up diagnostic hysteroscopy did not demonstrate any change in the direction or the magnitude of the effect size. The authors concluded that in everyday clinical practice the application of ACP gel may be considered in the specific subgroup of women undergoing D&C for miscarriage with at least one D&C in their history. These women are at an increased risk of clinically relevant adhesion formation, and prevention of IUAs is essential to obtaining good reproductive outcomes. Additional studies are needed to confirm the present findings as well as the impact of using ACP gel on long-term and patient important reproductive outcomes such as live-birth, pregnancy, and miscarriage rates.

Hooker et al. (1) have conducted a sound clinical trial in women with proven fertility at high risk of IUAs. Infertile women undergoing intrauterine surgery constitute a second subgroup at risk of a negative impact on their reproductive performance related to IUAs—it seems logical that they may benefit of the use of ACP gel as well. The body of evidence on the effectiveness of antiadhesion treatment for improving key reproductive outcomes or for decreasing IUAs after operative hysteroscopy in infertile women remains uncertain, as published in a Cochrane review on this topic (2). The quality of the evidence retrieved was low or very low for all outcomes. The Cochrane reviewers concluded that additional studies are needed to assess the clinical effectiveness of different antiadhesion therapies for improving reproductive outcomes in infertile women treated by operative hysteroscopy. This is consistent with the findings of the Hooker study.

It is imperative that more studies should be designed, but the PAPA trial provides yet another example of a problem often encountered by enthusiastic clinical researchers in the field of surgery: the recruitment period was longer than anticipated, and the number of recruiting centers had to be increased during the study to reach the needed sample size. Problematic recruitment is only one of a multitude of barriers that clinical researchers involved in designing surgical trials have to face (3, 4): problems of the surgical learning curve, differences in surgical expertise, difficulty in standardizing surgical interventions, problems of blinding in surgical trials, the presence of cointerventions, and issues of statistical power calculation.

We agree with Hooker et al. that at the research level we need long-term follow-up evaluations of randomized controlled trials reporting the key outcomes that matter to women: live-birth, pregnancy, and miscarriage rates. We suggest that at the level of society cost-effectiveness trials should be designed to compare the balance of clinical benefits and adverse events (effectiveness) as well as the comparative health costs associated with the use of different treatment strategies. Although the time may not have come to radically change clinical practice, the gynecologic community should agree upon the future decisions to be made. The body of evidence upon which to base a change in practice (evidence-based practice) is still too small at the present. On the other hand the available evidence is informative enough to direct both future research and clinical practice (evidence-informed practice). Evidence-informed decision making involves integrating the best available research evidence into the decision-making process. Additional factors—community health issues and local context, community and political preferences and actions, and public health resources—create the environment in which that research evidence is interpreted and applied.

The model for evidence-informed decision making is particularly relevant at the fifth step of evidence-informed practice: adapting the information to a local context (5). At the patient level we should inform women at high risk of IUAs (two or more D&C in the history) or at high risk of a negative impact of IUAs (infertile women bound to undergo operative hysteroscopy) that applying ACP gel may decrease the occurrence and the extent and severity of IUAs compared with no treatment. When in doubt about the balance of pros and cons (clinical equipoise), participation in a pragmatic multicenter, randomized controlled trial could be offered as an alternative.

At the level of public health it may be time to implement change as well. In Belgium, for instance, at present antiadhesion barrier gels are in use to prevent adhesions after surgery under specific codes, which can only be employed when the product was used in a woman younger than 40 who wishes to become pregnant; after an intervention by laparoscopy or laparotomy, only a limited number of exclusive codes are available. There is at the present no reimbursement for using ACP gel after any surgical intervention by hysteroscopy. Given the burden of IUAs both for the individual at-risk patient and for society, the reimbursement for applying ACP gel after operative hysteroscopy should be negotiated with the health authorities and the health insurance institutions.

Clinically and scientifically sound studies like the PAPA trial should make us both proud and confident about the future of clinical research in gynecologic surgery. Finding proof of effectiveness and aiming to help individual women in making "evidence-informed" decisions has become a cornerstone in gynecology on which we can build a strong edifice of scientific surgery at the service of individuals and society.

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