Reduction of postoperative adhesion development

Michael P. Diamond, M.D.

Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta University, Augusta, Georgia

Despite use of meticulous surgical techniques, and regardless of surgical access via laparotomy or laparoscopy, postoperative adhesions develop in the vast majority of women undergoing abdominopelvic surgery. Such adhesions represent not only adhesion reformation at sites of adhesiolysis, but also de novo adhesion formation at sites of surgical procedures. Application of antiadhesion adjuvants compliment the benefits of meticulous surgical techniques, providing an opportunity to further reduce postoperative adhesion development. Improved understanding of the pathophysiology of adhesion development and distinguishing variations in the molecular biologic mechanisms from adhesion-free peritoneal repair represent future opportunities to improve the reduction of postoperative adhesions. Optimization of the reduction of postoperative adhesions will likely require identification of unique, personalized approaches in each individual, representing interindividual variation in peritoneal repair processes. (Fertil Steril® 2016;106:994–7. ©2016 by American Society for Reproductive Medicine.)

Key Words: Adhesion development, adhesion reformation, antiadhesion adjuvants, de novo adhesion formation, postoperative adhesions

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/11946-reduction-of-postoperative-adhesion-development

Postoperative adhesion development remains a major adverse consequence of gynecologic surgery (and surgery elsewhere throughout the body). Although the specific consequences vary depending on the surgical site, they include bowel obstruction, pain, enhanced rate of injury at subsequent surgical procedures, interference with physiologic and mechanical organ function, and increased repeat operative time with associated increased cost (1, 2).

Currently, there remains an inability to accurately identify the occurrence, anatomic sites of involvement, and characteristics of adhesions (filming versus dense, avascular versus vascular, and bands versus cohesive) through the use of biomarkers or imaging studies. Although some groups have reported identification of adhesions by ultrasound in combination with mechanical manipulation, such approaches have not been widely reproduced and do not provide comprehensive identification of the location, incidence, and characteristics of adhesions. Thus, currently direct visualization of the adhesions at the time of a second-look surgical procedure is required to reproducibly and accurately characterize postoperative adhesion development (3).

Consequently, the ability to assess contributions to adhesion reduction by the method of access to the surgical site, the use of instrumentations or procedures, and/or administration of antiadhesion adjuvants requires surgical paradigms/models that encompass sequential surgical procedures. Among the diverse models that have been used are neonatal staged cardiothoracic procedures for congenital heart disorders, colectomy with ileostomy, and gynecologic procedures related to preexisting adhesions, endometriosis, ovarian cysts, and uterine fibroids. However, the majority of efficacy studies assessing the ability to reduce postoperative adhesion development have used gynecologic models (e.g., pelvic side wall, myomectomy, ovarian cystectomy, adhesiolysis, and treatment of endometriosis) in women desiring future fertility.

To appreciate the mechanism(s) for benefit of the approaches (including the use of antiadhesion adjuvants) to reduce postoperative formation and reformation of adhesions, it is important to understand the pathophysiology of peritoneal repair and the pathophysiology that leads to adhesion development (4–7). Briefly, after surgical tissue injury, there is local release of histamine, cytokines, and growth factors. The effects of these compounds include the initiation of local tissue inflammation processes, which initiates capillary leakage of serosanguineous fluid including clotting factors, and recruitment of macrophages and other cells, including fibroblasts. Cutting, fulguration, and ligation of the macrovasculature and microvasculature leads to a state of tissue hypoxemia, along with the accumulation of

Received June 9, 2016; revised and accepted August 11, 2016.
M.P.D. is a consultant with Actamax, Evidera, and Temple Therapeutics.
Reprint Requests: Michael P. Diamond, M.D., William H. Brooks, MD, Distinguished Chair Professor and Chair, Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta University, 1120 15th Street, BA-7300, Augusta, Georgia 30912 (E-mail: Michael.diamond@augusta.edu).

Fertility and Sterility® Vol. 106, No. 5, October 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.08.029

metabolic byproducts such as lactic acid, the lowering the pH of the injured tissue, and the conversion from aerobic to anaerobic metabolism within the injured tissues. Other processes affected include plasminogen activator activity (PAA) (a function of tissue plasminogen activator and its inhibitor, plasminogen activator inhibitor-1), metalloproteinase activity, and extracellular matrix deposition (such as collagen 1, collagen 3, and fibronectin). There is also initiation of processes leading to angiogenesis, which can lead to new vessel formation that could resupply oxygen to these tissues as well as remove metabolic byproducts (4–7).

Tissue hypoxia also results in creation of oxidative stress, with production of oxygen and nitrogen free radicals, which can result in DNA mutations, alterations of mitochondrial DNA, and generation of oxidized proteins (6). The free radicals produced include superoxide ($O_2^{\bullet -}$) generation from the reduced form of nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase, which can exert these effects, or through a rapid reaction with nitric oxide (NO) can yield peroxynitrite ($ONOO^-$), with subsequent reaction with this thiol and iron sulfur centers leading to lipid peroxidation and protein nitration. Furthermore, dismutation of superoxide forms hydrogen peroxide (H_2O_2), which can either combine with chloride ions from myeloperoxidase to form hypohalous acids, or react with superoxide to form the highly reactive hydroxyl radical ($HO^{\bullet}$). These free radicals, also enhance the expression of many of the factors involved in the inflammatory-like response that leads to adhesion development, including type 1 collagen, transforming growth factor $\beta 1$, tumor necrosis factor α, interleukin 6, and vascular endothelial growth factor (6). Of note, the scavenging of free radicals such as superoxide by superoxide dismutase can prevent the development of the adhesion phenotype (8). Other antioxidants that may also scavenge free radicals and diminish development of the adhesion phenotype include catalase, glutathione, omega-3 fatty acids, and lycopene (6, 9, 10).

A key facet of whether peritoneal repair occurs with or without adhesion development (adhesion formation or reformation) is the magnitude of the proteinaceous mass (blood and serosanguineous fluid resulting in a fibrin clot) that accumulates at the site of tissue injury (11). The larger the mass, the greater the likelihood of adhesion development. Other key factors are [1] PAA at the site (which resides not only in mesothelial cells as previously thought, but also in fibroblasts) which regulates degradation of the fibrinous mass, and [2] the degree and extent of tissue hypoxia, which regulates PAA and other components of the inflammatory response to tissue injury (4–7). Consistent with these considerations, Ivarsson et al. (12) identified that plasminogen activator inhibitor-1 levels were increased and tissue plasminogen activator activity reduced in patients with severe adhesions as compared with patients who had less severe adhesions.

If the proteinaceous mass persists long enough to allow fibroblast migration into the fibrin clot, extracellular matrix will be deposited, with the resulting development of an adhesion. In contrast, if fibroblast migration is stopped at the injured tissue surface (because of lack of a bridging fibrinous mass to an adjacent tissue surface), then deposition of extracellular matrix may cause fibrosis of the tissue, but no adhesions connecting tissue surfaces at nonanatomic locations will develop. It is important that the time for remesotheliazation of the peritoneum (or the bridging adhesion) is thought to be no more than 3 to 5 days. Thus, in the absence of factors that prolong the healing process, adhesion development or healing without adhesions will occur in this same 3- to 5-day window. An important corollary of this understanding of peritoneal repair is that surgical approaches to reduce postoperative adhesion development, including antiadhesion adjuvants, need to be present or exert their effects over only this brief 3- to 5-day time period to be effective.

It is important to recognize that after adhesiolysis, adhesion development occurs regardless of whether the procedure is conducted at laparotomy (13–15) or laparoscopy (16), with percentages of often 80% of patients or more (13, 14, 16). In fact, in approximately 10% of individuals the incidence, extent, and severity of adhesion actually increase after surgical procedures, even when they are conducted by experienced surgeons using what are considered to be optimized surgical techniques (14). Often underappreciated is that the same high incidence, extent, and severity of adhesion development occur in spite of how the procedures are performed, as seen in studies by individuals generally considered to be highly experienced and respected gynecologic surgeons, and despite the use of "microsurgical" techniques. The tenets of gynecologic microsurgery include minimization of tissue handling, achievement of meticulous hemostasis, avoidance of site desiccation, and precise approximation of tissue surfaces. Application of the principles of gynecologic microsurgery, whether the procedures are performed by laparotomy or by laparoscopy, remains a key approach to minimization of postoperative adhesion development, the efficacy of which is supplemented by the use of antiadhesion adjuvants.

In the United States, only three products that have been approved by the U.S. Food and Drug Administration (FDA) for the indication of reducing postoperative adhesion development remain available for clinical use (Supplemental Table 1, available online) (1). All are considered (and are regulated) as devices. All three separate opposing peritoneal surfaces during the aforementioned critical 3- to 5-day period of remesotheliazation. Thus, this represents the time period that antiadhesion adjuvants (or any biologic effects an adjuvant may have) need to persist to be efficacious.

The first antiadhesion adjuvant approved by the FDA for the indication of reducing postoperative adhesion development was Interceed (Johnson & Johnson), which is composed of oxidized regenerated cellulose. Specifically, the "Gynecare Interceed Absorbable Adhesion Barrier is indicated as an adjuvant in open (laparotomy) gynecologic pelvic surgery for reducing the incidence of postoperative pelvic adhesions after meticulous hemostasis is achieved consistent with microsurgical principles." This material is a woven fabric that is placed on the traumatized tissue and then moistened to assist with its adherence to the tissue. The material gelates within approximately 8 hours after application, with closure (filling-in) of the interstices between fibers. Much of the material is gone within 4 days in animal studies. In the presence

of blood, the material turns dark brown or black; in animal studies this was associated with loss of efficacy.

The pivotal clinical trial that led to the approval of Interceed was conducted for laparotomy in women with bilateral pelvic sidewall adhesions (17). After completion of the surgical procedure, including adhesiolysis and attaining meticulous hemostasis, one sidewall was randomized to be covered with the adjuvant while the contralateral side remained untreated. Thus, each woman was able to serve as her own control. Efficacy was assessed at the time of an early second-look laparoscopy. On the control sidewall, in association with the use of good surgical technique alone, the sidewall adhesion score was reduced approximately 25% from the initial score. In contrast, a significantly greater reduction in adhesion score, representing a decrease of approximately 50%, was observed after the use of good surgical technique plus the adjuvant. Subsequently, other studies have investigated the efficacy of oxidized regenerated cellulose, including in women with endometriosis and after ovarian and tubal surgery (18). Results demonstrating efficacy of a similar magnitude on control and adjuvant-treated sites were observed. This product is not approved in the United States for use after laparoscopic surgical procedures.

The second product approved by the FDA was Seprafilm (Sanofi-Aventis), which is composed of hyaluronic acid and carboxymethylcellulose that have been modified to prolong their retention time in the body before resorption. The material is a thin, fairly brittle film that adheres to tissue when placed. Two pivotal trials (19, 20) were conducted concurrently that led to approval by the FDA, with an indication that states that "Seprafilm Adhesion Barrier is indicated for use in patients undergoing abdominal or pelvic laparotomy as an adjunct intended to reduce the incidence, extent and severity of postoperative adhesions between the abdominal wall and the underlying viscera such as omentum, small bowel, bladder, and stomach, and between the uterus and surrounding structures such as tubes and ovaries, large bowel, and bladder."

In the gynecologic study, women underwent a myomectomy at laparotomy. At the conclusion of the procedure, women were randomized to have the product applied over the anterior and posterior uterine surfaces or to have no coverage. Efficacy was again assessed at the time of an early second-look laparoscopy. Use of this adjuvant was associated with a 36.8% reduction in the mean number of anatomic sites adherent to the uterus (20). The second concurrent study was conducted in men and women undergoing colectomy for ulcerative colitis or familial polyposis, with creation of a temporary ileostomy (19). The adjuvant was placed on the omentum and small bowel underlying the anterior abdominal wall incision in half the patients (assigned in a randomized fashion). A second-look examination to assess adhesions to the anterior abdominal wall was conducted at the time of taking down the jejunostomy and reestablishment of bowel patency. Among the control patients, anterior abdominal wall adhesions were observed in 94% of individuals. In contrast, among those who received the antiadhesion adjuvant there was a highly statistically significant reduction in anterior abdominal wall adhesions as well as a reduction in the severity of adhesions that did develop (19). In the general surgical patients, there was a small but not statistically significant increase in abscess formation in the adjuvant-treated patients; no such difference was observed in the gynecologic surgical patients.

The third antiadhesion adjuvant approved and available for use in the United States is Adept (Baxter), which is an icodextrin solution. "Adept Adhesion Reduction Solution is indicated for use intraperitoneally as an adjunct to good surgical technique for the reduction of postsurgical adhesions in patients undergoing gynecological laparoscopic adhesiolysis." In the pivotal U.S. trial, women were randomized to use of this product or not for irrigation throughout the procedure, with additional instillation of the agent at procedure completion. Efficacy was again assessed at the time of a second-look laparoscopy, at which time there was observation of a 9.8% difference in the incidence of adhesion development (21). Further, among the 24 sites evaluated, there was an average reduction of less than one site per subject in adjuvant-treated woman. However, in a follow-up, randomized clinical study of this agent of over an additional 400 women, no statistically significant reduction in postoperative adhesion development was observed (22).

The commonality among each of these three adjuvants is their function as a barrier physically separating opposing tissue surfaces either by application to a surface or by a hydroflotation effect. Each device also is present only transiently, either due to degradation, resorption, or absorption. Thus efficacy is considered to be related to physical tissue separation during the time period of remesotheliazation.

It is important that the next generation of antiadhesion adjuvants may manifest efficacy by multiple pathways. First they will be a device (barrier) separating tissues during peritoneal repair. A second mechanism will be that the barrier could serve as a method of local delivery of a drug or biologic. Such approaches would take advantage of molecular biologic differences between normal peritoneum and either injured peritoneum or sites of pre-existing adhesions with adhesiolysis (23). Such an approach would allow local actions of these agents so as to limit systemic effects after parental administration.

Recognition of the molecular biologic processes and pathways that enhance adhesion development also provides the opportunity to identify individuals with polymorphisms or epigenetic changes that promote (or reduce) the propensity for postoperative adhesion development. Such considerations introduce the possibility for a "personalized medicine" approach to identify individuals (or locations) at greatest risk for adhesions as well as find individualized selective pathways that could be targeted to minimize or prevent postoperative adhesion development.

REFERENCES

1. Diamond MP, Wexner SD, diZereg GS, Korell M, Zmora O, Van Goor H, et al. Adhesion prevention and reduction: current status and future recommendations of a multinational interdisciplinary consensus conference. Surg Innov 2010;17:183–8.
2. Awonuga AO, Fletcher NM, Saed GM, Diamond MP. Postoperative adhesion development following cesarean and open intra-abdominal gynecological operations: a review. Reprod Sci 2011;18:1166–85.

3. Fortin CN, Saed GM, Diamond MP. Predisposing factors to post-operative adhesion development. Hum Reprod Update 2015;21:536–51.
4. Diamond MP, Freeman ML. Clinical implications of postsurgical adhesions. Hum Reprod Update 2001;7:567–76.
5. Saed GM, Diamond MP. Molecular characterization of postoperative adhesions: the adhesion phenotype. J Am Assoc Gynecol Laparosc 2004; 11:307–14.
6. Awonuga AO, Belotte J, Abuanzeh S, Fletcher NM, Diamond MP, Saed GM. Advances in the Pathogenesis of Adhesion Development: The Role of Oxidative Stress. Reprod Sci 2014;21:823–36.
7. Braun KM, Diamond MP. The biology of adhesion formation in the peritoneal cavity. Semin Pediatr Surg 2014;23:336–43.
8. Fletcher NM, Jiang ZL, Diamond MP, Abu-Soud HM, Saed GM. Hypoxia-generated superoxide induces the development of the adhesion phenotype. Free Radic Biol Med 2008;45:530–6.
9. Victory R, Saed GM, Diamond MP. Antiadhesion effects of docosahexaenoic acid on normal human peritoneal and adhesion fibroblasts. Fertil Steril 2007; 88:1657–62.
10. Fletcher NM, Awonuga AO, Saed MG, Abu-Soud HM, Diamond MP, Saed GM. Lycopene, a powerful antioxidant, significantly reduces the development of the adhesion phenotype. Syst Biol Reprod Med 2014;60:14–20.
11. Saed GM, Fletcher NM, Diamond MP. The Creation of a Model for Ex Vivo Development of Postoperative Adhesions. Reprod Sci 2016;23:610–2.
12. Ivarsson ML, Bergstrom M, Eriksson E, Risberg B, Holmdahl L. Tissue markers as predictors of postoperative adhesions. Br J Surg 1998;85:1549–54.
13. Diamond MP, Daniell JF, Martin DC, Feste J, Vaughn WK, McLaughlin DS. Tubal patency and pelvic adhesions at early second-look laparoscopy following intraabdominal use of the carbon dioxide laser: initial report of the intraabdominal laser study group. Fertil Steril 1984;42:717–23.
14. Diamond MP, Daniell JF, Feste J, Surrey MW, McLaughlin DS, Friedman S, et al. Adhesion reformation and de novo adhesion formation after reproductive pelvic surgery. Fertil Steril 1987;47:864–6.
15. Trimbos-Kemper TC, Trimbos JB, van Hall EV. Adhesion formation after tubal surgery: results of the eighth-day laparoscopy in 188 patients. Fertil Steril 1985;43:395–400.
16. Operative Laparoscopy Study Group. Postoperative adhesion development after operative laparoscopy: evaluation at early second-look procedures. Fertil Steril 1991;55:700–4.
17. Azziz R. Microsurgery alone or with INTERCEED absorbable adhesion barrier for pelvic sidewall adhesion re-formation. The INTERCEED (TC7) Adhesion Barrier Study Group II. Surg Gynecol Obstet 1993;177:135–9.
18. Wiseman DM, Trout JR, Franklin RR, Diamond MP. Metaanalysis of the safety and efficacy of an adhesion barrier (Interceed TC7) in laparotomy. J Reprod Med 1999;44:325–31.
19. Becker JM, Dayton MT, Fazio VW, Beck DE, Stryker SJ, Wexner SD, et al. Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: a prospective, randomized, double-blind multicenter study. J Am Coll Surg 1996;183:297–306.
20. Diamond MP. Reduction of adhesions after uterine myomectomy by Seprafilm membrane (HAL-F): a blinded, prospective, randomized, multicenter clinical study. Seprafilm Adhesion Study Group. Fertil Steril 1996;66: 904–10.
21. Brown CB, Luciano AA, Martin D, Peers E, Scrimgeour A, diZerega GS, et al. Adept (icodextrin 4% solution) reduces adhesions after laparoscopic surgery for adhesiolysis: a double-blind, randomized, controlled study. Fertil Steril 2007;88:1413–26.
22. Trew G, Pistofidis G, Pados G, Lower A, Mettler L, Wallwiener D, et al. Gynaecological endoscopic evaluation of 4% icodextrin solution: a European, multicentre, double-blind, randomized study of the efficacy and safety in the reduction of de novo adhesions after laparoscopic gynaecological surgery. Hum Reprod 2011;26:2015–27.
23. Ambler DR, Golden AM, Gell JS, Saed GM, Carey DJ, Diamond MP. Microarray expression profiling in adhesion and normal peritoneal tissues. Fertil Steril 2012;97:1158–64. e1–4.

SUPPLEMENTAL TABLE 1

Antiadhesion adjuvants approved for gynecologic use by the U.S. Food and Drug Association and currently available for clinical use.

Product composition	Type of procedure indicated for use by U.S. FDA
Oxidized regenerated cellulose	Laparotomy
Modified hyaluronic acid and carboxymethylcellulose	Laparotomy
Icodextrin solution	Laparoscopy

Diamond. Postoperative adhesion reduction. Fertil Steril 2016.