Reduction of postoperative adhesion development

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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;■:■–■. ©2016 by American Society for Reproductive Medicine.)

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

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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.
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Fertility and Sterility® Vol. ■, No. ■, ■ 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