MASTER CLASS

Pelvic Adhesions – An Update

CHARLES E. MILLER, M.D.

"A number of human interventional trials and animal studies have evaluated techniques and materials designed to prevent and reduce postsurgical adhesions. The results have been inconclusive and sometimes contradictory. Thus, preventing postsurgical adhesions remains an art, rather than a science." So I began my introduction to the program on adhesion prevention at the 2010 Congress of the Society of Laparoscopic Surgeons in New York City.

Patients with adhesions can present with small bowel obstruction or with complaints of infertility, chronic pain, or dyspareunia. Unfortunately, adhesive disease is problematic. Four percent of the patients undergoing abdominal and pelvic surgery will be readmitted due to adhesion-related complications. In excess of 400,000 surgical procedures are performed annually in the United States for lysis of adhesions. In a Scottish National Health Service Study of nearly 9,000 women who previously underwent open gynecologic surgery, just less than 3% were readmitted secondary to adhesions; the highest readmit rate was ovarian surgery (BJOG 2000;107:855-62).

While one would expect a reduction in the number of patients undergoing laparoscopic surgery, in reality, the verdict is not yet clear. A 1998 meta-analysis showed a decrease in both reformed (26.6% vs. 14.3%) and de novo adhesions (45.2% vs. 37.2%) in the laparoscopic group, compared with laparotomy (Fertil. Steril. 1998;70:702-11).

Despite this, other authors cite pneumoperitoneum, prolonged surgery, high insufflation pressure, and overzealous use of energy to cut and coagulate as reasons why laparoscopic surgery increases risk of adhesions.

The economic impact of adhesions is staggering, in excess of $1.3 billion in the United States per year.

For this current excerpt of the Master Class in Gynecologic Surgery, I have solicited the wisdom of Dr. Michael Diamond. He is the Kamran S. Moghissi Professor of Obstetrics and Gynecology and associate chairman of the department of obstetrics and gynecology at Wayne State University, Detroit. Dr. Diamond also is director of the division of reproductive endocrinology and infertility and assistant dean for clinical and translational research at the university. Dr. Diamond has spent much of his academic career involved in the pathogenesis, prevention, and treatment of pelvic adhesions. He is truly considered the world's leader in this area, and we are honored to have Dr. Diamond as guest author of this important area of our surgical arena. ■

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The Where and Why of Postsurgical Adhesions

The prevention of postsurgical adhesions is one of the greatest unmet needs in medicine today. Surgical series have shown that adhesions are present after 80%-90% of abdominal and pelvic surgeries, and that these abnormal fibrous connections have a tremendous propensity to reform after adhesiolysis. (We will define adhesions here as "attachments between surfaces at nonanatomical locations.")

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In gynecologic surgery, postoperative adhesions are a frequent cause of infertility, pain, bowel obstruction, and difficulty in later procedures. Adhesions can occur after minimally invasive procedures, which have the potential for trocar injury to structures adherent to the anterior abdominal wall. Other intraoperative injuries can occur due to obscured normal anatomy or restricted access. A significant number of patients also undergo second surgeries to treat sequelae that are directly related to adhesions.

The literature is replete with studies of adhesion development and reports of its incidence and its consequences. Still, the problem of postoperative adhesion development often goes underestimated or unrecognized. This is because we don't routinely perform early second-look operations to assess adhesion development, and because there are no serum markers or sensitive imaging techniques to allow their identification. In addition, we do not follow our patients who seek care from other providers as insurance coverage changes or as other health problems arise, such as bowel obstruction being treated by a general surgeon.

As gynecologic surgeons, we must appreciate that while infections, endometriosis, and other peritoneal insults may contribute to adhesion development, surgery is the most common cause. We also must appreciate how tissue injury leads to the development of adhesions, and why adhesion reformation so commonly occurs.

This understanding is critical to our consideration and use of the "barrier" products currently available for reducing postsurgical adhesions – and critical to our efforts to employ the tenets of gynecologic microsurgery and to achieve as optimal a surgical outcome as possible. At this point in time, use of approved surgical adjuvants in combination with good surgical technique offers the best chance at adhesion reduction and prevention.

Incidence of Adhesions

A series of reports published in the early to mid-1980s documented how commonly adhesions develop after various types of reproductive pelvic surgery. Through early second-look laparoscopy, postoperative adhesions were found to occur, in these studies, in 55%-100% of patients after their primary gynecologic surgery.

In a multicenter study published in 1987, my colleagues and I also showed that gynecologic surgeries performed at the time of laparotomy are frequently complicated by both adhesion reformation and de novo adhesion formation. More than half of the 161 women (51%) who had a second-look laparoscopy 1-12 weeks after reproductive pelvic surgery were found to have de novo adhesion formation (adhesions in at least one new location). Adhesion reformation was also widespread: At the initial laparotomy, 121 of the patients (all of whom were treated for infertility) were noted to have some form of adhesion, and adhesion reformation subsequently occurred at the site of adhesiolysis in 85% of these women, with no differences with respect to adhesion type (Fertil. Steril. 1987;47;864-6).

It was hoped, and largely expected, that the growth of laparoscopy and minimally invasive surgery approaches in more recent years would reduce postoperative adhesion development – that minimally invasive techniques would prove to be less adhesiogenic than laparotomy. Questions remain, but thus far, such hopes have diminished and our expectations for significant improvement have gone unsubstantiated.

One multicenter study on adhesion development after initial laparoscopic procedures found that the incidence of adhesions at an early second-look procedure was 97% – no lower than in prior reports of second-look laparoscopy after laparotomy.

In this study, 68 women underwent operative laparoscopic procedures, including adhesiolysis, and had second-look procedures within 90 days. The good news was that de novo adhesion formation between the two laparoscopic procedures occurred in only 8 of the women (12%) and at 11 of 47 possible sites – much less frequently than after laparotomy. Adhesion scores also decreased at the second look compared with the status of the pelvis at the initial procedure. Still, with the high rate of adhesion reformation, almost all of the women developed postoperative adhesions.

Thus, even when the initial procedure was performed laparoscopically, adhesion development was an all-too-common occurrence, and appeared to be independent of the character of the initial adhesion (Fertil. Steril. 1991;55:700-4).

More recently, data from randomized studies of various adhesion barriers and potential anti-adhesion adjuvants have further dashed hopes that laparoscopy per se can reduce adhesion development.

For instance, in a recent small pilot study of a fibrin-based product called Adhexil, "control" ovaries that were not treated had a 27% increase in the mean adhesion score between an initial laparoscopic procedure and second-look laparoscopy. The women in the study had undergone bilateral ovarian surgery, with ovaries randomized for application of the product or no treatment (Fertil. Steril. 2011;95:1086-90). Clearly, a laparoscopic approach to their procedures did not prevent the development of adhesions.

Many of the initial studies on adhesion development were comprised of patients with infertility, but more recent observations have been extended to women without infertility and to men. Studies have covered patients undergoing colectomies, for instance, as well as neonates undergoing cardiothoracic procedures.

In a recent review article on adhesion prevention and reduction, members of an interdisciplinary consensus conference stated that adhesions develop after "nearly all" abdominal and pelvic procedures performed through either standard laparotomy or laparoscopic approaches. With respect to gynecologic surgery, they point out, research has shown that the most common site for postsurgical adhesion development is the ovary (Surg. Innov. 2010;17:183-8).

Consequences

Pelvic adhesions are a well-recognized cause of infertility, contributing to up to an estimated 40% of the cases of infertility in women. Adhesions are also a leading cause of bowel obstruction and a significant cause of chronic or recurrent pelvic pain.

The contribution of pelvic adhesions to chronic pelvic pain is not completely understood. Adhesions may be the cause of pain in some women, and in other women, an incidental finding that is not contributing to pain. In patients who have endometriosis as well, the question remains as to the contribution of endometriosis per se, or adhesions, to the pain. Endometriosis can cause adhesions and chronic pelvic pain, presumably

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through the cyclic generation of inflammatory molecules.

The relationship between chronic pain and adhesions is further complicated by ensuing questions about the efficacy of adhesiolysis. The two randomized trials that have thus far examined the role of adhesiolysis in the reduction of chronic pelvic pain failed to demonstrate a significant improvement in pain after adhesiolysis; however, the high failure rates after follow-up may be due to adhesion reformation and de novo adhesion formation (Fertil. Steril. 2004;82:1483-91). Performance of more randomized comparisons in the future may yield improved outcomes when adhesiolysis is paired with postprocedure use of anti-adhesion adjuvants.

Despite the uncertainties, multiple studies support the current estimation that adhesions cause or significantly contribute to chronic pelvic pain in up to 30% of women with the problem. As the Ovarian Adhesion Study Group noted in one of its reports, adhesions have been reported as a primary cause of chronic pelvic pain in 13%-36% of women, depending on the study (Obstet. Gynecol. 1995;86:335-40). Economic analyses also have quantified the impact of adhesion-related hospital readmissions. A study done in the United Kingdom, for instance, concluded that 6% of all hospital readmissions in patients who had undergone abdominal or pelvic surgery were directly related to adhesions (Lancet 1999;353:1476-80). Another report on hospitalizations for lower abdominal adhesiolysis in the United States estimated that in 1988, the cost of adhesions stemming from gynecologic procedures alone was almost $1.2 billion. This estimate did not include outpatient and indirect costs (Surg. Gynecol. Obstet. 1993;176:271-6).

Why, How Adhesions Develop

Our current understanding is that adhesions develop as a result of injury to and devascularization of the peritoneum, and the subsequent inflammatory response and peritoneal wound healing process. Tissue hypoxia triggers a cascade of intracellular responses that, in combination with the fibrinous collection of blood and serosanguinous fluid at the tissue surface, may result in adhesion development.

In the initial postsurgical period, either overt bleeding or oozing may occur at the site(s) of tissue injury, forming clots. In combination with serosanguinous fluid, which may leak from damaged peritoneal surfaces, a fibrinous mass thus develops at the surgical sites and sites of tissue injury. This represents an initial step in peritoneal repair.

When surrounding tissue is normal and there is a sufficient amount of plasminogen activator present in the peritoneum – and when numerous other events and conditions are optimal – the resulting fibrinous mass can be degraded. As that occurs, and tissue healing continues, fibroblasts are recruited to the surface of the injury site from underlying tissues.

If the fibrinous mass is no longer present, fibroblasts "stop" at the tissue surfaces, and become covered by mesothelial cells which line the peritoneal surface as the process of remesothelialization occurs. This process appears to be initiated within hours after surgery and is generally believed to be completed in 3-5 days. (In such instances, healing would have occurred without adhesions, although subperitoneal fibrosis may have occurred.)

Various hypoxia-driven responses, however, such as a reduction in plasminogen activator activity, can cause the fibrinous mass to persist during the healing process, before remesothelialization occurs. In this case, fibroblasts migrate not only to, but through, the injury site, and into the persisting fibrinous mass. This is subsequently followed by deposition of collagen, fibronectin, and other extracellular matrix materials – creating the beginnings of a true adhesion.

In such cases, remesothelialization still occurs, but the mesothelial cells cover the adhesion as well as the normal tissue surfaces, forming adhesive bands and other types of connections between opposing serosal tissue surfaces. Angiogenesis then occurs as the hypoxic tissue in the adhesion sends signals (such as vascular endothelial growth factor) in an attempt to reestablish a supply of oxygen and nutrients to the injured and devascularized tissues. Subsequently, as the tissue remodels, there is a propensity for the adhesion to become more vascular and denser.

Understanding this process is important because the products currently available for reducing adhesions act as barriers during this critical period of remesothelialization, keeping peritoneal surfaces apart and minimizing the potential development of a fibrinous mass that bridges tissue surfaces. If an adhesion does not form during the 3-5-day period of remesothelialization, it is theorized that there will not be any adhesion development – unless there's new injury to the tissue surfaces.

Once an adhesion forms, however, it has acquired a particular "adhesion phenotype" – different from that of normal peritoneum – that appears to be irreversible. This is likely why it is so difficult to prevent adhesion reformation after adhesiolysis. Rates of adhesion reformation – even in the best of surgical hands – run between 80% and 90%, compared with a 50% chance of de novo adhesion development after surgery (at new sites of injury).

The identification of an adhesion phenotype came originally from comparisons of normal peritoneal and adhesion tissues harvested from the same patient, and were later confirmed in cell culture studies in which normal peritoneal fibroblasts were subjected to hypoxia (2% O_2 conditions). Fibroblasts cultured under hypoxic conditions were subsequently found to have developed particular molecular biologic characterizations that are different from those of normal peritoneal fibroblasts.

When exposed to normal amounts of oxygen again, the fibroblasts did not go back to being normal fibroblasts – they continued to manifest the adhesion phenotype (J. Am Assoc. Gynecol. Laparosc. 2004;11:307-14). These findings have been confirmed in animal and human studies, and such relationships have also been identified in other peritoneal tissue types such as mesothelial cells and macrophages.

Further research on the pathogenesis of adhesions and the molecular biologic differences between normal peritoneum and adhesions may allow identification of which patients, and which sites within a patient, are most at risk for adhesion development, as well as the discovery of new ways to reduce the development of postoperative adhesions and their clinical sequelae.

It is possible that a future generation of barrier products not only will work as a barrier separating surfaces prior to remesothelialization, but will also have local biologic effects – delivering adhesion-reducing drugs or biologics, for instance, to specific localized tissue sites. A personalized approach to adhesion prevention also might be possible, with particular factors deemed to increase adhesion risk in individual patients (a deficiency of plasminogen activator, for instance) being corrected.

In the meantime, as we've learned more about the pathophysiological state under which adhesions develop, we have found that adhesion development may occur faster than we had thought. In one recent rodent study, we identified postoperative tissue attachments as early as 2 hours after cecal abrasion. We noted considerable local edema and vessel dilatation within 2 hours of injury, angiogenesis and fibrin deposition at 8 hours, and cell proliferation at 24 hours (Fertil. Steril. 2010;93:2734-7). And interestingly, recent studies in mice have shown that laparoscopic insufflation per se can induce peritoneal adhesions, with the adhesions increasing proportionally with both increasing duration of insufflation and an increase in intraperitoneal pressure.

Prevention in Practice

During the past decade a variety of surgical adjuvants – from procoagulants and fibrinolytic agents to anti-inflammatory drugs and antibiotics – have been investigated for use in reducing the occurrence, extent, and severity of adhesions. Unfortunately, most approaches seemingly have been futile. Some products have shown trends toward efficacy in animal or early human studies and need further investigation.

The three synthetic products that are approved by the Food and Drug Administration– Gynecare Interceed, Seprafilm, and Adept – can help reduce postoperative adhesions after gynecologic procedures, and should be considered as potentially useful surgical adjuvants. A meta-analysis of studies of Gynecare Interceed, for instance, found that approximately twice as many operative sites were adhesion free after use of the barrier than after surgery alone (J. Reprod. Med. 1999;44:325-31).

Gynecare Interceed (Johnson & Johnson) and Seprafilm (Genzyme) are approved for use only at laparotomy, while Adept (Baxter International), an icodextrin solution that disperses throughout the abdominopelvic cavity, is approved for use only in laparoscopic surgery.

The key consideration to make when using Interceed – a biodegradable woven fabric composed of oxidized, regenerated cellulose – is the importance of achieving meticulous hemostasis. Its efficacy is reduced, or can even be lost, in the presence of blood. Care also must be taken not to stretch the material or alter its shape and the spacing between the weaves. Otherwise, the material, once gelated, will have a greater potential for spaces in which the tissue surfaces would not be separated and thus a greater potential for blood coagulation and fibroblast in-growth. Multiple pieces of the material may be overlapped, but there have been no benefits demonstrated (at least in animal studies) to using double layers.

Care in application also is critically important for Seprafilm, a film composed of modified hyaluronic acid and carboxymethylcellulose. Seprafilm is brittle and is difficult to apply through small incisions. While it's not impossible to deliver the product laparoscopically, many surgeons have found this very difficult. And in the United States, it is approved for use with laparotomy only.

In applying Seprafilm, it is critical to first get good exposure of the field and then position the film very carefully. Attempts to reposition the product will often result in tears or breaks. Of course, just as with Interceed, this device is believed to work primarily by separating tissue surfaces, and thus it has little to no chance of success if it does not completely separate the surgically injured tissue from other tissue surfaces in the initial postoperative period while remesothelialization is occurring.

The use of adjuvants, moreover, is no substitute for good surgical technique that aims to minimize tissue injury, tissue devascularization, and inflammation. This is easier to achieve, of course, during a microsurgical procedure such as a tubal anastomosis than in a patient with severe endometriosis or many large fibroids. Still, to the extent possible for the procedure being conducted, the tenets of gynecologic microsurgery should always be considered:

► Handle as little tissue as possible, as minimally as possible. To the extent possible, handle only those portions that will subsequently be excised.

► Keep tissues moist. Tissue drying leads to injury and loss of mesothelial cells. Raw surfaces are more prone to develop adhesions.

► Take special care in the use of suture. Consider whether clinical situations will allow use of less reactive and smaller-caliber suture. When using suture to tie off blood vessels, skeletonize the vessels so as to minimize the amount of tissue distal to the suture that will become hypoxic and serve as a nidus to adhesion development.

► Target the use of electrosurgery and other energy sources. Use it in specific localized sites where it's needed, such as to stop bleeding, but avoid widely dispersed use, when possible, again to minimize the amount of residual devitalized tissue remaining in the pelvis at the conclusion of the surgical procedure. ■

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