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Review Article

Postoperative Adhesions as a Consequence of Pelvic Surgery

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ABSTRACT Adhesions represent a frequent thought-provoking surgical ramification that greatly affects clinical practice, thereby making adhesion deterrence an important area of public health intervention, research, and the fiscal budget. Postoperative adhesions have been observed in up to 94% of patients after laparotomy. Adhesion-related readmissions, 1 year after surgery, were found to be in 1.3% to 1.5% of the therapeutic and diagnostic laparoscopic procedures. This systematic review looks at gynecologic experience with the management of postoperative adhesions and related complications and recommends intervention when data permits. Journal of Minimally Invasive Gynecology (2015) 22, 549–563 © 2015 AAGL. All rights reserved.

Keywords: ADEPT; Adhesions; Bowel obstruction; Hypoxia; Infertility; Inflammation; Interceed; Laparoscopic; Seprafilm

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Adhesions are defined as abnormal fibrous connections between anatomic surfaces. They develop as a result of inflammatory processes such as infections and inflammation; endometriosis; and most frequently secondary to surgical trauma after incision, cauterization, suturing, or other disruption of the tissue infrastructure. To mitigate adhesion development, strategies including the reduction of peritoneal damage, prevention of coagulation of serous exudate, resolution of fibrin deposits, inhibition of fibroblast activities, prevention of collagen deposits, and separation of peritoneal surfaces during remesothelialization have been proposed.

Meticulous surgical practices, which are the hallmark of microsurgery, are of benefit and may rectify the adhesion dilemma although the extent to which these techniques decrease this disorder remains unclear. Potential sequelae of adhesions after surgical procedures include infertility [1], pain [2], bowel obstruction [3], and difficult repeat surgical procedures [4]. The most common site for adhesions after female pelvic surgery is the ovary [5]. Ensuing surgery often subjects the surgeons to difficulties with access and obscured anatomy, which may lead to an inability to use minimally invasive surgical techniques, prolongation of operative time, or potentially serious organ injuries such as enterotomy [6].

The management of adhesions includes their related complications (hospital stay, readmissions, and potential litigation), which have a significant impact on the health care system. Calculated yearly, health care costs for adhesion-related admissions in the United States are $2.25 billion [7,8]. Thus, postoperative adhesions represent a frequent thought-provoking surgical ramification that greatly affects clinical practice, thereby making adhesion deterrence an important area of public health intervention, research, and the fiscal budget. Despite the gravity and prevalence of the problem, only limited progress has been made in either prevention or treatment.

Epidemiology and Incidence

Postoperative adhesions have been observed in up to 94% of patients after laparotomy. There are many studies showing the frequency and magnitude of the consequences of postoperative adhesions, which demonstrate the need for strategies to rectify the impact that this disorder has on society [9].

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The Surgical and Clinical Adhesions Research Group has studied the data from the Scottish National Health Service Medical Record Linkage to record the incidence of complications associated with adhesions after surgery. The database was analyzed to develop a cohort of 8849 women who underwent open gynecologic surgery in 1986, and then all of their readmissions in the subsequent 10 years were reviewed for potential related disorders. The rate of readmission directly related to adhesions was 2.9% of the initial operations, and ovarian surgery had the highest rate directly related to adhesions (7.5% of the initial operations). Twenty percent of the admissions were within 1 year of the initial procedure, and 4.5% were for bowel obstruction [10]. Studies have shown that up to 93% of patients who have undergone laparotomy will develop adhesions [11], and 55% to 100% of women who have undergone gynecologic laparoscopic surgery will develop postoperative adhesions.

It has been suggested that, because of the less invasive nature of laparoscopic surgery, postoperative adhesions occur less frequently than after open surgery [12]. Another study reported adhesion-related readmissions were observed in 10% of surgical patients within 5 years, and there is a 20% lifetime risk of requiring further hospitalizations [13]. One of the limitations of this study remains the lack of stringent long-term follow-up on these patients. Directly, adhesion-related readmissions, 1 year after surgery, were found in 1.3% to 1.5% of the therapeutic and diagnostic laparoscopic procedures. Readmission rates for laparotomy after surgery on the fallopian tubes were 0.9%, for ovaries they were 2.1%, and for the uterus they were 0.6% [14].

Pathogenesis

There are a number of facets involved in adhesion development. Injury to peritoneal surfaces initiates a repair response consisting of an inflammatory process and bleeding, resulting in local hypoxia that perpetuates endothelial permeability with serosanguineous tissue exudation and lymphatic leakage. The disruption of stromal mast cells by the hostile environment causes release of vasoactive substances including histamines, kinins, growth factors, and inflammation. These result in the foundation of a fibrin clot overlying the injured tissue.

Pathological bonds are created between surfaces, enabling the basal membrane of the mesothelial layer to adhere to the neighboring tissues. Fibrin is deposited that contains exudates of cells, leukocytes, and macrophages. This process occurs within 3 hours after injury; the transient exudates can be degraded by fibrinolysis within 72 hours. Normal tissue repair is facilitated by this exudate, which attracts invading fibroblasts and angiogenesis. With complete fibrinolysis and reabsorption of degradation products, re-epithelialization will result without evidence of adhesions.

Adhesions are the result of tissue trauma in which a subsequent torrent of events occurs, including fibrinolytic activity that is compromised (Diamond et al, 1998), fibrinous mass persisting, and fibroblast ingrowth occurring with deposition of extracellular matrix (ECM) material. An abnormal connection between tissue surfaces (likely vascularized) develops that forms adhesions [15], which consequently is altered by the plasminogen system. Tissue injury leads to a hypoxic state, which is an important advocate to modifying the cascade of responses that ultimately progresses to the development of postoperative adhesions.

A reduction in plasmin promotes increased adhesion establishment by altering fibrinolysis [16]. Plasminogen activator activity (PAA), a process that is suppressed by local trauma, regulates the presence of this structure. In a normal scenario, the tissue plasminogen activator system presents in the peritoneal mesothelium, and its underlying fibroblasts function to remove the fibrinous gel matrix [17]. PAA, which is represented by the ratio of tissue plasminogen activator to its plasminogen activator inhibitor-1, resides in both the peritoneal mesothelial cells and the underlying fibroblasts. PAA endures typically with dissolution of the fibrinous mass by fibrinolysis for 72 hours [17]. The activated fibroblasts are removed by apoptosis [18], allowing tissue to heal without inappropriate attachments to other tissues. With trauma and subsequent flow of events, fibrinolytic activity is compromised (Diamond et al, 1998), the fibrinous structure remains, and fibroblast ingrowth occurs with deposition of ECM material including collagen, which forms atypical connections between tissue to form adhesions [15]. With local hypoxia enduring, it initiates a series of gene signaling pathways that may result in alteration of the balance between ECM deposition and degradation. Adjacent fibroblasts proliferate, become myofibroblasts, deposit collagen matrix, and migrate toward the site of tissue injury and promote adhesion development [19]. Imbalance between fibrin deposition and fibrinolysis is the key driver in the development of postoperative adhesions [20].

Several molecular biologic annotations have been made in recent years comparing normal peritoneum and adhesion fibroblasts, with the characterization of an “adhesion fibroblast phenotype.” Cellular metabolism has been shown to be a key factor in the pathogenesis of postoperative adhesions [21]. Current data show that uncoupling oxidative phosphorylation with DNP promoted the adhesion phenotype within a hypoxic and normoxic state (the environment was not the critical factor in this pathway) as established by an increase in both type I collagen and vascular endothelial growth factor (VEGF) levels in human fibroblasts isolated from normal peritoneal tissue [116]. Collagen deposition and angiogenesis are important components of the infrastructure for postoperative adhesion formation. VEGF is part of the pathway of dissemination of endothelial cells and thus is a major component of the angiogenesis process [22].

Teleologically, adhesions are known to develop as a response to hypoxia wherein the body tries to restore oxygen and nutrient supply to tissues that have been violated [15]. Hypoxia-mediated production of reactive oxygen species

(ROS), such as superoxide ($O_2^{\bullet -}$), seems to be a major factor in the development of postoperative adhesions [23]. An increase in ROS after laparotomy and laparoscopy has been documented in previous articles [24]. At a molecular level, superoxide has been shown to increase type I collagen levels in normal peritoneal and adhesion fibroblasts [23]. The hostile inflammatory background can effect ROS, which are free radical molecules that are highly caustic to cellular functions [25]. ROS and reactive nitrogen species are known to contribute to vascular dysfunction and remodeling through oxidative impairment by reducing the bioavailability of nitric oxide (NO), marring endothelium-dependent vasodilatation and endothelial cell growth, causing apoptosis, stimulating endothelial cell migration, and activating adhesion molecules [26]. Hypoxia has also been revealed to play a role in the creation of these free radicals both in vivo and in vitro. Adhesion development is contingent with an annoyance in the tightly controlled balance between ROS production and elimination, either via the expansion of ROS generation or defective/deficient antioxidant fortifications for their elimination.

Tissue hypoxia during surgery is an important component in the development of the adhesion phenotype and induces proliferation while inhibiting apoptosis in fibroblasts from adhesions [15,27]. There is an increase in extracellular matrix production and a decrease in degradation of the matrix inhibitors leading to a milieu that favors an adhesion phenotype that has an increase in collagens, fibronectin, and transforming growth factor beta 1 (TGF-β1) [28]. Reactive radicals are produced after oxygen supply interruption and/or restoration and have been implicated in a number of signal transduction pathways such as NO and superoxide. The justification for a possible cross talk between iNOS and MPO in adhesion fibroblasts arises from the recent finding that the MPO/H_2O_2 system can efficiently consume NO released by iNOS during steady-state catalysis, thereby averting the NO-induced inhibition ascribed to the formation of the iNOS-nitrosyl complex in vitro. By altering iNOS and MPO gene expression, small interfering RNA was shown to significantly reduce type I collagen and TGF-β1, hallmarks of the adhesion phenotype. Studies show that MPO is differentially expressed and colocalized with iNOS in normal peritoneal and adhesion fibroblasts where they play a central role in the development of the adhesion phenotype. Silencing the expression of iNOS resulted in a significant inhibition in type I collagen and TGF-β1. Also, there is interplay between markers of postoperative adhesions (type I collagen and TGF-β1) and modulators of free radicals (iNOS and MPO). The induction of MPO expression during hypoxia may have beneficial effects in preventing the development of the adhesion phenotype [29]. Fluctuating the balance between NO production and NO scavenging in response to hypoxia exposure in peritoneal fibroblasts may contribute to the development of the adhesion phenotype [30]. Hypoxia-inducible factors also up-regulate genes involved in cell growth, cell survival, and angiogenesis [31]. Mitochondrial dysfunction created by surgically induced tissue hypoxia can lead to the creation of ROS and reactive nitrogen species as well as antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase, which when optimal have the potential to abrogate the abnormal milieu, preventing the cascade of events leading to the development of adhesions in injured peritoneum [32]. One study elaborately showed that adhesion fibroblasts exhibit lower apoptosis and higher protein nitration compared with normal peritoneal fibroblasts [15] (Figs. 1 and 2).

A molecular biomarker study with postoperative adhesions using microarray expression profiling was undertaken and documented that tissue-specific gene expression was not reflected by the presence/absence of unique genes but rather by the specific number of copies of the genes expressed. Accordingly, alterations in gene expression that are functionally relevant to the pathophysiology of postoperative adhesions are not clearly understood (National Center for Biotechnology Information). A majority of the genes were identified in adhesion tissue function as regulators of cell survival, cell and tissue, cell motion, and other components of biological pathways. The nature of adhesion development and growth is vastly different from that of normal peritoneal tissues; therefore, it was speculated that the outcome of their tissue characteristics is influenced in part by the products of genes regulating cell growth and apoptosis, inflammation, angiogenesis, and tissue turnover and may also be under different tissue-specific regulatory control. These data may be used to develop therapeutic targets aimed at limiting postsurgical adhesions [115].

Consequences of Adhesion Development

The devastating consequences of adhesion establishment include fertility abnormalities, the development of pain, dyspareunia, and intestinal obstruction (SRS, 2007). A substantial morbidity risk associated with surgery is readmission secondary to adhesions [10]. In gynecologic surgical procedures, pelvic adhesions can be seen within 2 to 3 days, and up to 56% to 100% of patients will experience adhesive disorders [33].

Infertility

The proposed adhesion pathway that affects infertility involves distortion of the adnexal anatomy and interference of the gamete and embryo transport. More severe adnexal adhesions are associated with worsening pregnancy rates, and treatment of adnexal adhesions appears to improve pregnancy rates. Among infertile women with adnexal adhesions, successful pregnancies were shown to be lower in women with untreated adhesions than in those who underwent adhesiolysis (16%–45% after 24 months) [34]. An early study looked at intrauterine pregnancy rates after adhesiolysis and showed a wide range from 38% to 57% [35].

Fig. 1

A proposed scheme for the pathogenesis of peritoneal adhesion development after injury. WBCs, white blood cells. From Awonuga AO, et al. Postoperative adhesion development following cesarean and open intra-abdominal gynecological operations: a review. *Reprod Sci.* 2011;18:1166-1185. Reprinted with permission.

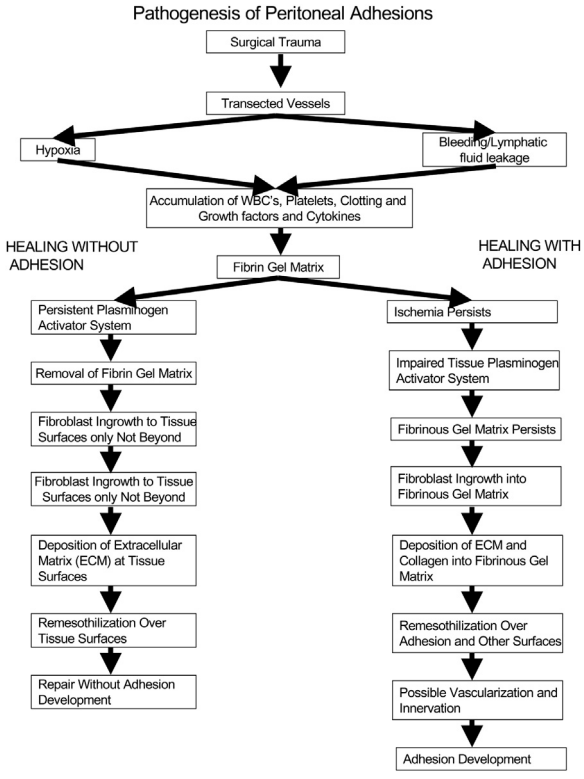
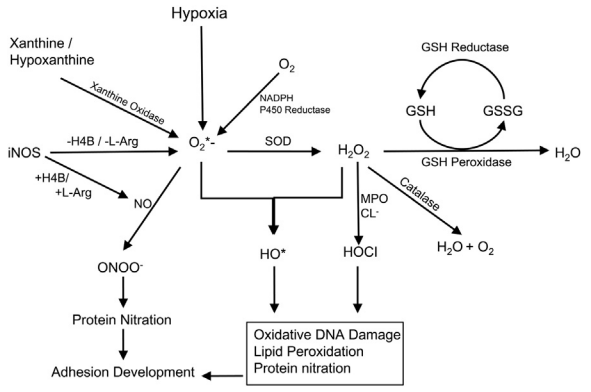


Fig. 2

A proposed scheme for the interaction of operative oxidative metabolic reaction and free radicals associated adhesion development. Cl^-, chloride ion; $Fe^{2þ}$ and $Fe^{3þ}$, elemental iron; GSH, glutathione; GSSG, glutathione disulfide; H4B, tetrahydrobiopterin; HOCI, hypochlorous acid; iNOS, inducible nitric oxide synthase; MPO, myeloperoxidase; O_2, molecular oxygen; $O_2^{\bullet -}$, superoxide anion; NADP, nicotine adenine dinucleotide phosphate; NO, nitric oxide; ROS, reactive oxygen specie; SOD, superoxide dismutase. From Awonuga AO, et al. Postoperative adhesion development following cesarean and open intra-abdominal gynecological operations: a review. *Reprod Sci.* 2011;18:1166-1185. Reprinted with permission.



A current meta-analysis of 10 studies including 1004 patients attempting pregnancy after colorectal surgery for inflammatory bowel disease, with a range in follow-up from 12 to 158 months, focused on unfavorable consequences from adhesions including female infertility and pregnancy rates and showed a bleak pattern. Pregnancy rates ranged from 38% to 65% after the surgeries compared with over 82% in the nonoperated group. A significant amount of the patients in the postoperative groups needed intervention with the infertility specialists [36]. Another study looking at adhesiolysis and infertility in a retrospective review evaluated unexplained infertility patients diagnosed with adnexal adhesions at laparoscopy. The pregnancy rates were 32% at 12 months and 45% at 24 months after subsequent adhesiolysis by laparotomy compared with 11% and 16%, respectively, in women left untreated [34]. In women followed for an average of 49 months after tubal surgery, term pregnancy rates were inversely correlated with adhesion scores as assigned using the American Society for Reproductive Medicine classification system for adnexal adhesions [37].

A study with significant power looked at infertility rates after laparoscopic ileal pouch-anal anastomosis (IPAA). This study found an infertility rate of 27% after total laparoscopic IPAA. The findings suggest that infertility rates are more advantageous after laparoscopic IPAA than after open IPAA [38].

A study following patients for 2 years assessed the effectiveness in pregnancy rates of microsurgery and operative laparoscopy in adhesiolysis. Adhesions were found to be the sole infertility factor in 15% of the patients in the investigation. Patients with periadnexal adhesions as the only cause of their infertility were treated by microsurgery or operative laparoscopy and were followed up for 24 months. The results indicate that advanced laparoscopic surgery is as beneficial as microsurgery in infertile patients with adhesions but offers some advantages in comparison with laparotomy. Factors that have a negative impact on the success rates are the rising age of the women, the increasing length in the time to attain fertility, and the worsening of the adhesions [39].

A prospective analysis of the proficiency of transvaginal ultrasonography (TVUS) in the screening of pelvic pathologies was performed to evaluate sonographic diagnosis with laparoscopic and pathological findings. The sensitivity of vaginal sonographic description of pelvic adhesions was 61.1% with a specificity and positive predictive value of 98.2% and 84.6%, respectively. The negative predictive value of TVUS was 94.1%. These statistics propose that it is not possible to depict pelvic adhesions, especially filmy adhesions, with acceptable accuracy. Nevertheless, in the initial examination of infertile women, if the patient is young and both hysterosalpingography and TVUS are negative, laparoscopy could be postponed [40].

Fig. 3

Postoperative bowel and uterine adhesions.

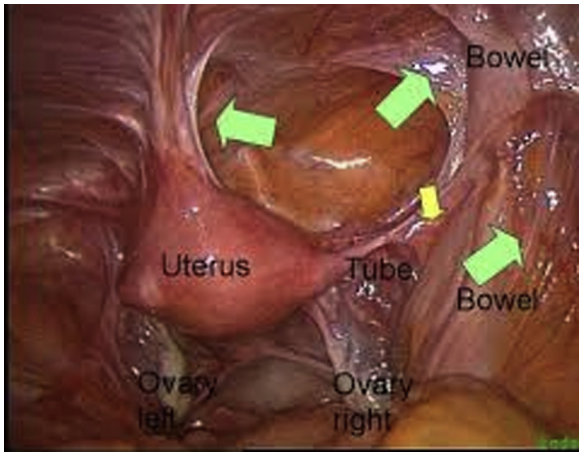
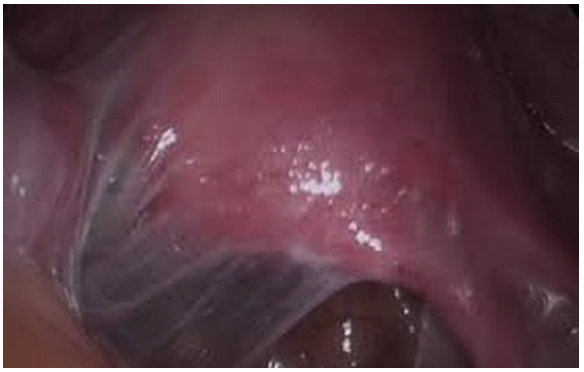


Fig. 4

Tubal and uterine adhesions secondary to pelvic surgery.



Bowel Obstruction

Adhesions are the most common culprit for postoperative small bowel obstruction. A recent systemic review with meta-analysis focused on the adverse sequelae from adhesions indicated the incidence of bowel obstruction was 9%, up to 3% to 4% had enterotomies after repeat abdominal surgeries, and from 40% to 47% of patients in 1 study had chronic abdominal and pelvic pain (ten Broek et al, 2013a).

In a series of 552 patients with bowel obstruction, intra-abdominal adhesions were considered to be accountable for this complication in 74% of the cases [41]. Canadian data from a retrospective analysis showed that abdominal hysterectomy was associated with adhesions and, subsequently, a significant risk of small bowel obstruction. The median interval between the initial operation and the small bowel obstruction was 5.3 years, which was similar to other studies for the 1998 to 2005 time period [42]. Small bowel obstruction after abdominal hysterectomy ranges between 13.6 and 16.3 per 1000 procedures [43]. Analysis of data from obstetric surgical interventions indicated only 5 per 10 000 cesarean deliveries were associated with bowel obstruction in contrast to the increased potential for gastrointestinal complications noted after gynecologic procedures. A nested case-control study of the Swedish Medical Birth Registry studied the risk for postoperative adhesions and intestinal obstruction after cesarean delivery. Women who had a cesarean delivery had an increased risk of adhesions (adjusted odds ratio = 2.1; 95% confidence interval) and intestinal obstruction (adjusted odds ratio = 2.0; 95% confidence interval, 1.7–2.4). It has been suggested that although the absolute risks of postoperative adhesions and intestinal obstruction after cesarean delivery are small, they should be included when counseling women concerning cesarean section [44,45].

The frequency of small bowel obstruction after surgery was assessed in 92 studies, and the rate by any cause was 9%. Adhesions seemed to be the most common cause of postoperative small bowel obstruction, accounting for 56%. The incidence of adhesive small bowel obstruction was 2.5% to 11.7% [46] (Fig. 3).

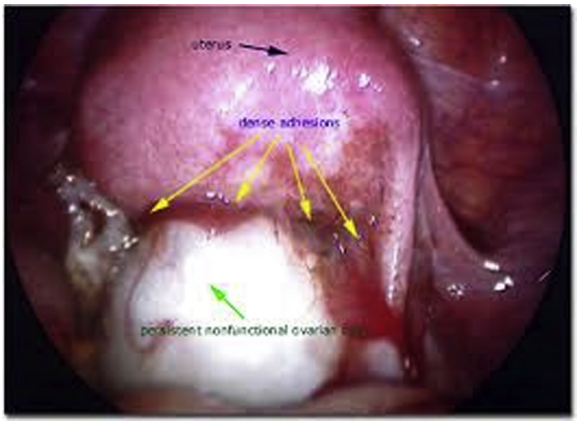
Abdominal/Pelvic Pain

Chronic pelvic discomfort may be associated with adhesions that limit organ mobility based on visceral pain fibers [47]. The relationship between adhesions and pelvic pain is unclear. In 1 study, patients were followed after lower gastrointestinal tract surgery for adhesive small bowel obstruction, and 40% developed chronic abdominal pain. In 4 studies following patients with chronic postoperative pain after previous surgery, adhesions were identified as the most likely cause of pain during diagnostic laparoscopy in over half of the patients. Dense bowel adhesions are linked with chronic pain. Visceral pain is connected with impairing organ mobility, but there is no association between the extent of adhesions and the severity of pain. Although nerve fibers have been identified in pelvic adhesions, their prevalence is no greater in patients with pelvic pain than in those without pelvic pain. It generally is accepted that adhesions may cause visceral pain by impairing organ mobility [48].

Involvement of the pelvic organs may be required to produce pain associated with adhesions [49]. Adhesions involving large or small bowel may have a decisive impact on pelvic pain in comparison with adhesions in other regions, especially in terms of recurrence of the disorder [50]. In a histologic analysis of adhesions associated with anatomic organs, it was determined that they were highly vascularized, containing well-developed arterioles, venules, and capillaries. Nerve fibers, with both myelinated and nonmyelinated axons, existed in adhesions from nearly two thirds of the studied patients. This study contests the notion that adhesions represent nonfunctional scar tissue and clearly establishes that adhesions are highly cellular, vascularized, and innervated, features more consistent with dynamic, regenerating entities. Several models have been suggested to explain the method by which adhesions cause pain; some scientists have proposed that pain could be

Fig. 5

Extensive pelvic adhesions.



caused by the stretching of the adhesion or the stimulation of the parietal peritoneum [51].

The impact that lysis of bowel or adnexal adhesions has on abdominal and pelvic pain resolution cannot be confidently predicted. In a randomized, controlled trial, 100 patients undergoing diagnostic laparoscopy for chronic pain ascribed to adhesions were recruited to test the hypothesis that adhesiolysis leads to substantial pain relief and improvement in quality of life. Participants were randomly allotted either to laparoscopic adhesiolysis or no treatment. Pain was evaluated for 1 year using the visual analog score. Both groups described significant pain relief and improved quality of life, but there was no difference between the groups [52]. A study comparing adhesiolysis (laparotomy) versus conservative management of patients with chronic pelvic pain found that adhesiolysis was effective only in those having adhesions involving the bowel. This subset had severe, vascularized, and dense adhesions of the intestinal tract. They had significantly less pelvic pain after adhesiolysis based on parameters including the McGill pain score, subjective pain assessment, and disruption of daily life. It has been suggested that surgical intervention is not recommended for light or moderate degree pelvic adhesions [48].

Reduction in Adhesion Formation

All surgeons must be accustomed with the risks and consequences of postoperative adhesions. The formation of postoperative adhesions may be limited by minimizing peritoneal injury during surgery, careful surgical technique, meticulous hemostasis, excision of necrotic tissue, minimizing ischemia and desiccation, and reducing the local inflammatory response by inhibiting the coagulation cascade and disseminating fibrinolysis. The subsequent healing process in the peritoneal cavity occurs by an association of mesothelial restoration and fibrosis, resulting in either re-establishment of the tissue serosa or adhesion formation [53] (Figs. 4 and 5).

The generally accepted method for preventing adhesion formation during surgery is minimizing surgical trauma. Despite the use of surgical adjuvants to reduce postoperative adhesion formation, adhesion development occurs and remains a conflicting dilemma [54]. A database review of 27 studies investigated the effect of various aspects of surgical technique on adhesion-related consequences. Findings were significant for an absence of any specific procedure that significantly reduced the incidence of adhesive small bowel obstruction. There was lowering of adhesions with minimally invasive surgery (laparoscopy) compared with laparotomies and when the peritoneum was not closed. The analysis showed no statistical evidence in promoting the surgical principles that using less invasive techniques, introducing less foreign bodies, or causing less ischemia reduces the extent and severity of adhesions in pelvic surgery [55].

Laparoscopy Versus Laparotomy

The laparoscopic approach to the abdominal cavity has been shown to cause less peritoneal and systemic immune responses compared with conventional techniques [56]. Presented data show that there is a significant migration of polymorphonucleocytes to the peritoneal cavity irrespective of the type of approach or the size of the incision. The inflammatory response to small abdominal incisions was comparable with that after laparoscopy, whereas longer incisions resulted in elevated interleukin 6 levels in several studies [57]. These findings suggest a higher immunologic impact of conventional surgery irrespective of the size of the abdominal incision. The supposition is that any approach to the peritoneal cavity causes local inflammatory responses. Peritoneal macrophage functions are more pronounced as well as systemic inflammatory responses in full laparotomy compared with minilaparotomy and laparoscopy [58].

Laparoscopy has historically been promoted to reduce adhesion formation compared with open surgery. Laparotomy has more inherent traumatic properties related to the incision line giving access to the operated organs, tissue disruption, direct hand manipulations, and increased tissue ischemia by suturing of the abdominal wound. Diminution or omission of some of these adverse effects may be overcome with minimally invasive surgical techniques although laparoscopy may cause a hostile environment because of the use of gas media to extend the abdomen [59]. Laparoscopy reduces de novo adhesion configuration but does not diminish adhesion reformation. Quantifying adhesion reduction does not necessarily have a statistically significant bearing on clinical outcomes. Broad peritoneal cavity fortification by insufflating a low-temperature, humidified gas mixture of CO_2, N_2O, and O_2 has been suggested to represent a possible approach for reducing peritoneal inflammation caused by CO_2 pneumoperitoneum [60]. In studies looking at animal models, endoscopic laser surgery did not

Table 1

Risk of postoperative adhesions with laparoscopy

Increased insufflation gas medium and flow rate	↑
Smoke and elevated intra-abdominal temperature	↑
Increased intra-abdominal pressure	↑
Pneumoperitoneum	↑
Humidified gas to prevent desiccation	↓

(Ott, 2008)

Table 2

Postoperative adhesion risks with cesarean delivery

	Primary cesarean delivery	Repeat cesarean delivery
Parietal peritoneal closure	↓	↑
Lower uterine segment, single-layer closure	↑	↑
Lower uterine segment, double-layer closure	↓	↓
Transverse closure of the uterus and peritoneum	↓	↓
Bowel obstruction risk compared with gynecologic surgery	↓	↓

statistically decrease the formation of postoperative adhesion compared with open surgery [61].

Studies show that, in the presence of a direct surgical trauma, the entire peritoneal environment is quantitatively the most important factor in adhesion formation and hence adhesion prevention after both open and laparoscopic surgery. Mesothelial hypoxia (CO_2 pneumoperitoneum) or hyperoxia (open surgery), desiccation, and surgical manipulation have been identified as factors cumulatively augmenting adhesion development. The clinical ramification is especially relevant for laparoscopic surgery because pneumoperitoneum, being a closed environment, can be easily conditioned [62].

The extent of tissue injury, not the surgical approach, is the determining factor in the initiation of the adhesion pathway. Experiments show that drying the surfaces of intra-abdominal structures leads to adhesion formation when in combination with serous material. Smoke and elevated intra-abdominal temperature may have an effect on peritoneal fibrinolysis [63]. Pneumoperitoneum has a tamponade effect although with desiccation of the peritoneum the risk for adhesion formation is enhanced. Other adverse effects of laparoscopy may be enhanced by increased intra-abdominal pressure, duration of the procedure, and insufflation gas [64]. It has been shown that there is a different morphologic effect of CO_2 pneumoperitoneum compared with laparotomy [65]. Using heated, humidified CO_2 in the rodent model decreases the risk of desiccation on the peritoneum during laparoscopy [66]. Adhesion scores increase with flow rate, hypoxia, and insufflation pressure of CO_2 pneumoperitoneum along with desiccation as a cofactor in laparoscopic-induced adhesion. Local TGF-β levels are affected by the intensity of light. The use of warmed humidified CO_2 has been shown to decrease adhesions in a mouse model. The pressure effects result in changes of intracellular and extracellular parameters regulating essential cell functions such as oxidative phosphorylation to produce adenosine triphosphate, cell proliferation, or onset of apoptosis, suggesting that it is not the chemical formula of the gas itself [67].

The Surgical and Clinical Adhesions Research Group looked at the effect of adhesions in a large population. In this review, there is agreement in showing limited benefits of laparoscopy on adhesion-related outcomes. The findings showed that open and laparoscopic gynecologic surgery is associated with comparable risks of adhesion-related readmissions [14]. Regardless of the surgical approach selected, procedures such as myomectomy often result in adhesions.

Minimally invasive surgery has a positive impact on the reduction of adhesion-related complications but does not totally prevent adhesion formation, contradicting the opinion that the use of antiadhesive barriers is not needed in laparoscopy. This observation highlights the propensity for postoperative adhesion development, which is present with both laparotomy and minimally invasive surgical techniques [5,68,69].

Laparoscopic adhesiolysis does not appear to reduce the amount of postoperative adhesion reformation compared with laparotomy procedures. However, some studies have implicated that laparoscopic reproductive pelvic surgery in various animal and clinical studies results in less recurrent and de novo adhesions as opposed to open surgical cases.

However, the most recent studies indicate small benefits of laparoscopy on adhesion-related outcomes compared with laparotomy [55]. Small bowel obstruction associated with adhesive disorders was lower after laparoscopic surgery in many studies that directly compared laparoscopic and open surgery. Laparoscopic supracervical hysterectomy was associated with a lower risk than abdominal hysterectomy when evaluating for gastrointestinal obstruction [42]. Patients undergoing second-look laparoscopy had a 12% de novo adhesion rate compared with a 51% de novo adhesion formation after laparotomy [5]. Follow-up endoscopic procedures such as laparoscopic myomectomies have shown a higher incidence of adhesions despite using a minimally invasive approach to the surgical process [70]. The incidence of postoperative infection, another risk factor for adhesion formation, is lower after laparoscopy than after laparotomy.

Currently, the best answer to adhesion development is attention to detail, adherence to microsurgical techniques, and thinking of adjuvants as complementing agents rather than a solvent for the correction of deficits. Intuitively, it seems that the benefit of the laparoscopic approach in surgery in diminishing adhesion risks is facilitated technically by using the least amount of tissue surface contact, minimizing intra-abdominal gas pressure, using decreased flow rates for pneumoperitoneum, and having humidified gas to

prevent desiccation [71]. Minimally invasive surgery does not totally prevent adhesion formation, and, thus, the use of antiadhesive barriers may be considered in laparoscopy [72] (Table 1).

Myomectomy

Regardless of the surgical approach, myomectomy often results in adhesions. The occurrence of adhesion has been reported to be greater than 90% after open abdominal myomectomy and up to 70% after laparoscopic myomectomy [73].

A survey during 2012 to 2013 was conducted among gynecologic surgeons to assess the actual knowledge and practice related to postsurgical adhesions and measures for reduction; 70.8% agreed that adhesions are a source of major morbidity. About two thirds informed their patients about the risk of adhesion. Most cited causes of adhesions were abdominal infections and extensive tissue trauma and endometriosis and myomectomy surgery. Knowledge of surgical techniques recommended and the use of antiadhesion agents developed to reduce adhesions need to be improved [74].

Parietal Peritoneal Closure

Whether parietal peritoneal closure is necessary or advisable remains controversial. Evidence suggests that the incidence of adhesions at the site of closure after laparotomy is approximately 22% with peritoneal closure and 16% without peritoneal closure. In women with ovarian cancer, closure of pelvic and periaortic peritoneum appears to result in greater adhesion formation than is observed when the dissected areas are left open. General surgeons have long abandoned the closure of visceral and parietal peritoneum based on the studies in oncology patients that suggested more adhesion development after closure [75]. In laparotomy, the parietal peritoneum, a layer of tissue that lines the inner wall of the abdomen, has to be opened before the abdominal cavity can be entered. By comparison, laparoscopy is keyhole abdominal surgery, which also involves opening the parietal peritoneum. There is no evidence for any short-term or long-term advantage in peritoneal closure for nonobstetric operations [76]. The effects of peritoneal closure with chromic catgut suture after reproductive surgery by Pfannenstiel incisions have also been studied clinically and by second-look laparoscopy [77]. These authors found no statistically significant difference in the rate of adhesion to the anterior abdominal wall between the group with peritoneal closure and the group without peritoneal closure.

The ideal surgical technique for performing a cesarean section in regard to diminishing the risk for postoperative adhesions remains a dilemma. Rates of adhesion development recorded at second and third cesarean deliveries range from 24% to 75% [78]. One prospective cohort study [79] of women undergoing their first repeat CD, irrespective of whether the visceral peritoneum was closed or not, found that after controlling for potential confounding variables, parietal peritoneal closure at primary CD was 5-fold protective against all adhesions and 3-fold protective against dense and filmy adhesions.

With the peritoneum left open, the enlarged postpartum uterus may disrupt the typical mesothelial matrix formation of peritoneal healing [79]. A database analysis showed that with transverse closure of the uterus, there was a statistically significant decrease of adhesions with peritoneum closure compared without closure [80].

Aside from peritoneal closure, the techniques used to close the hysterotomy incision in the lower uterine segment and propensities for bladder adhesions have also been studied. Blumenfeld et al [81] from Stanford University found that single-compared with double-layer closure was associated with a 7-fold increase in the odds of developing bladder adhesions. However, bladder adhesions were not influenced by visceral or parietal [81] peritoneal closure (Table 2).

Evidence in the literature suggests that the consequences of postoperative adhesions as they relate to bowel obstruction [43], infertility [82], and chronic pain [83] may be less after cesarean delivery compared with gynecologic surgery. This presents a dichotomy because hematologic and vascular changes with pregnancy have a propensity for decreased fibrinolysis [84], which theoretically should increase the incidence risk for development. Further studies should continue to interrogate the reasoning for less pregnancy-associated adhesions despite a theoretical increased propensity for adhesions after cesarean delivery based on biological models [85].

Adjuncts to Surgical Technique

A compelling upstream factor of an injured peritoneum such as oxidative stress may have downstream implications for adhesion development. Antiadhesion adjuvants with an ability to reduce postoperative adhesions on a local level as well as acting as a physical barrier to separate tissues during the early phase of healing would theoretically mitigate the adhesive disorder [54]. This proposed pathway involves a physical barrier remaining in place to retard migration of the proliferating fibroblasts at the tissue edge and promote remesothelialization to occur over the traumatized surfaces without adhesion development bridging adjacent tissue surfaces. Healing occurs by this combination of fibrosis and mesothelial regeneration [86].

Pathogenesis of the postoperative adhesion formation was investigated in various studies, and several agents have been examined for the prevention of adhesion formation. There have been a variety of surgical adjuvants investigated to assess their efficacy to reduce the occurrence, extent, and severity of adhesion development including procoagulants, fibrinolytic agents, anti-inflammatory drugs, antibiotics, and mechanical barriers (films, gels, and liquids, which are either absorbable or nonabsorbable) [5,54,87,88]. A number of local and systemic anti-inflammatory drugs and

adhesion-reducing substances, including dexamethasone and promethazine, have been evaluated along with antibiotic solutions and crystalloid solution instillates without any evidence they reduce postoperative adhesions.

Antiadhesion barriers typically function by separating tissue surfaces during reperitonealization, which is thought to be initiated within hours of a surgical injury and completed within 3 to 5 days [89]. Barriers to prevent adhesion are not regularly used despite their ability to reduce the severity of adhesion formation. A systematic review and meta-analysis searched for randomized controlled trials assessing the use of oxidized regenerated cellulose, modified hyaluronate carboxymethylcellulose, icodextrin, or polyethylene glycol in abdominal surgery. Reoperation for adhesive small bowel obstruction was the main outcome. Oxidized regenerated cellulose reduced the incidence of adhesions along with evidence indicating that hyaluronate carboxymethylcellulose reduces the incidence of reoperations for adhesive small bowel obstruction [90].

Three synthetic products, Interceed, Seprafilm, and ADEPT Adhesion Reduction Solution, are approved for clinical use in the United States indicated for the reduction of postoperative adhesions but with limited success [91]. None of the preapproval studies of adhesion-prevention products have reported clinical outcomes such as pregnancy rates, pain, or small bowel obstruction as the primary end point in their pivotal studies. There is evidence that the use of barriers such as Interceed and Seprafilm in women of reproductive age undergoing conservative surgery in order to conceive will have a reduction of adhesion formation after laparoscopy or laparotomy [54]. Surgical barriers may help to decrease postoperative adhesion formation but cannot compensate for poor surgical technique. One study compared the most commonly used adhesion barriers against a control group in a clinically relevant rat model after being exposed to electrosurgery and suturing. Subsequently, the experimental lesions were treated with Seprafilm, ADEPT, Intercoat, Spraygel, or no barrier. The resulting adhesions were examined 14 days postoperatively. There were statistically significant differences between the barriers with regard to the area covered by adhesions and the adhesion-free incidence. Despite this, a significant adhesion burden remains with all of the tested barriers [91].

The compositions of these synthetic products are all different. Interceed is a fabric composed of oxidized regenerated cellulose, Seprafilm is a film composed of modified hyaluronic acid and carboxymethylcellulose, and ADEPT is an icodextrin solution that disperses throughout the abdominopelvic cavity. Interceed and Seprafilm are currently approved for treatment in laparotomies, and ADEPT has Food and Drug Administration (FDA) approval for use in laparoscopy. However, despite the biochemical differences, all these products have in common their reported primary mode of action as a barrier. The pathophysiology of their mode of action is by separating the operative tissue from other surfaces while remesothelialization is occurring during the subsequent 3- to 5-day postprocedure period [5].

In 1 retrospective cohort chart reviewed, the effectiveness of an absorbable adhesion barrier used at primary and repeat cesarean deliveries was evaluated. Of 262 primary cesareans performed, 43% (n = 112) had a repeat cesarean section. With a barrier, 74% had no adhesions at repeat surgery versus 22% in the no barrier group (p = .011). Eleven percent had grade 2 adhesions with a barrier, whereas 64% had grade 2 to 3 in the no barrier group (p = .012). The barrier group had no grade 3 adhesions. Those with parietal peritoneal closure had less incidence (p = .02) and mean adhesion severity (p = .03); no significant difference was found per suture type. Thus, they concluded that the use of an absorbable adhesion barrier diminishes the frequency and severity of adhesions at cesarean [92].

Different synthetic adhesion barriers are promoted as a means of reducing adhesion formation resulting from cesarean delivery. There have been only 2 small, nonblinded, and nonrandomized trials, both of which had a small power and subject to bias. There was no improvement in significant clinical outcomes. As a matter of fact, intra-abdominal adhesions from prior cesarean delivery infrequently cause maternal impairment and have not been shown to negatively affect perinatal sequel [93].

The 2 studies in which adhesion barriers were used during cesarean delivery are methodologically flawed because they had small sample sizes and allocation to treatment groups was not random and seemingly not blinded. Fushiki et al compared 27 cases of repeat cesarean delivery in which the clear film adhesion barrier had been placed at the time of the primary cesarean section. At the subsequent cesarean section, adhesions were present in 2 of 27 cases in the Seprafilm group and 12 of 25 cases in the control group. There were no differences in blood loss or any measured meaningful clinical outcomes between the groups.

The second study by Kim et al is a report of only 8 patients in whom the absorbable adhesion barrier was placed at the time of the primary cesarean section. At the subsequent cesarean section, none of the patients in the Interceed group had detectable adhesions, whereas all patients in the control group had adhesions. There were no significant differences in the surgical procedural time or blood loss in either of the groups.

A 2008 Cochrane Review assessing the effectiveness of different adhesion barriers at the time of gynecologic surgery found that “the absorbable adhesion barrier Interceed reduces the incidence of adhesion formation after laparoscopy and laparotomy,” but there are insufficient data to support its use to improve pregnancy rates.

Based on the review of the available literature, there does not appear to be strong evidence suggesting that the use of adhesion barriers at cesarean delivery is merited at the present time. The very limited data on the implementation of such barriers at cesarean delivery fail to support any meaningful short-term clinical benefit, including

decreasing the risk of visceral injury at repeat cesarean sections [94].

Seprafilm

Seprafilm adhesion barrier is a bioresorbable membrane composed of chemically modified sodium hyaluronate and carboxymethylcellulose that was approved by the FDA in 1996. The product is indicated for use in abdominal or pelvic laparotomy and is intended to reduce the incidence, extent, and severity of postoperative adhesions.

The safety and efficacy of Seprafilm were evaluated in 2 multicenter clinical trials. In 1 investigation, patients undergoing colectomies were enrolled [95]. At second-look procedures, an absence of adhesions was observed in 51% of Seprafilm-treated patients, whereas only 6% of control patients had no adhesions to the anterior abdominal wall. In a second randomized trial, 127 women undergoing uterine myomectomy were included [33]. Postoperative adhesion formation was evaluated during second-look laparoscopy performed an average of 23 days later. Seprafilm was applied to the anterior and posterior uterus after myomectomy. Using the American Society for Reproductive Medicine score as 1 of the end points, the application of this product resulted in a significant reduction in the incidence of adhesions to the uterus.

Seprafilm labeling has been updated to warn against wrapping directly around a newly created anastomotic suture or staple line. Additionally, the results of 1 cost-effectiveness study are encouraging, but more investigation is warranted. Further studies are needed to delineate the molecular biologic processes leading to normal peritoneal healing as opposed to adhesion development, which would allow targeted interventions to improve adjuvant efficacy [96].

An initial pilot clinical trial of laparoscopic application of Sepraspray Adhesion Barrier, a modified hyaluronic acid and carboxymethylcellulose powder (Genzyme Bio Surgery), for the reduction of postoperative adhesions after myomectomy was organized. In studies conducted to date, there does not appear to be a biologic effect of modified hyaluronic acid and carboxymethylcellulose, which are the components of Seprafilm Adhesion Barrier and Sepraspray Adhesion Barrier, on adhesion development. Sepraspray Adhesion Barrier showed clear efficacy trends in the reduction of adhesions to the anterior and posterior uterus and the proportion of patients with either side of the uterus free from dense adhesions at second-look laparoscopy [97]. The efficacy of Sepraspray has not been completely evaluated by the FDA, and this product is not available for use in the United States. The safety and efficacy of Seprafilm use have been established in abdominopelvic surgery. A retrospective investigation from the result of a randomized controlled trial advocates that enfolding Seprafilm around a newly created anastomosis may be associated with an increase in anastomotic leak–related adverse events [96].

Fushiki et al performed a prospective cohort study with Seprafilm placement at the time of the primary cesarean section and assessment at the repeat cesarean delivery. The incidence and severity of adhesions were significantly reduced in the Seprafilm group compared with the control group (7.4% vs 48%, which was statistically significant). In this study of women receiving Seprafilm at their first cesarean section, up to 93% of the patients were adhesion free, resulting in decreased procedure and delivery times at repeat cesarean sections. For procedures such as myomectomies and cesarean deliveries in which blood loss and contamination of the operative arena are predictable, the specialist should be cognitive of the effect of blood or inflammation on the adhesion-prevention barrier [98].

Interceed

The FDA approved Interceed in 1989 for open gynecologic pelvic surgery for adhesion control. In subsequent studies of Interceed applied to organs at both laparoscopic and open procedures, a reduction in the incidence of both new and reformation of adhesions was reported although it was not statistically significant [99]. There was a 32% reduction in the incidence of adhesions to the pelvic sidewall when compared with microsurgical techniques alone [100]. Meticulous control of bleeding is required for the optimum benefit from this adhesive barrier [101,102]. Oxidized regenerated cellulose (Interceed) is another absorbable adhesion barrier. There is scant evidence that the reduction in adhesions resulting from the use of Interceed improves fertility. Interceed is a procoagulant and causes fibrin deposition at sites of incomplete hemostasis. Although its primary mode of action is considered a barrier separating injured tissue surfaces, oxidized regenerated cellulose inhibits hydrogen peroxide production by macrophages and competes with LPS for the scavenger receptors on macrophages, thus potentially reducing the release of inflammatory mediators, cellular growth factors, and the secretion of matrix components that are promoters of the adhesion fibroblast [92,103].

In a small Korean study, Interceed was used for adhesion reduction after cesarean sections, and the results showed a reduction in the amount of adhesions in the Interceed group. Meticulous hemostasis is required and may limit the use of this product with cesarean sections. A retrospective cohort chart review of primary and subsequent first repeat cesarean sections was evaluated for adhesions with and without an adhesion barrier. There were less adhesions with parietal peritoneal closure and a significant reduction in adhesions. Findings showed that the use of an absorbable adhesion product reduces the incidence and severity of adhesions at cesarean sections. A follow-up economic study looked at using an adhesion barrier as the standard of care in a cesarean model. Assuming 1000 cesarean births took place in the model year, with 500 complicated by adhesions, the total cost of adhesions to the facility would be $1 807 500 per year, and using Interceed would produce a cost savings of $837 500 per year [92].

ADEPT

ADEPT is approved for the reduction of postsurgical adhesions in patients undergoing gynecologic laparoscopic adhesiolysis. ADEPT is an adhesion-prevention barrier consisting of icodextrin 4% solution that may be introduced during laparoscopy.

A multicenter pilot study looked at the efficacy of this barrier for protection from adhesion production in women undergoing laparoscopic gynecologic surgery. Its reported efficacy is a 9.8% reduction in incidence compared with controls [104]. The biological components of ADEPT are consistent with a water-soluble, high-molecular-weight, alpha (1,4)-linked glucose polymer in an electrolyte composition. When used as a peritoneal instillate (1–1.5 L), 4% icodextrin's task as a colloid osmotic agent is to retain fluid within the peritoneal cavity for an interval of 3 to 4 days. Icodextrin is transported into the systemic circulation via peritoneal lymphatic drainage and processed by alpha-amylase to lower molecular-weight oligosaccharides that are eliminated by renal excretion. A systematic review concluded that there was a lack of evidence for its use as an adhesion-preventing agent (Metwally et al, 2006).

The objective of a recent study was to assess the efficacy of ADEPT in decreasing adhesions during laparoscopic gynecologic surgery. Patients were randomized during laparoscopy to either have ADEPT or lactated Ringer solution (LRS). Over four hundred patients returned for a second laparoscopy within 4 to 8 weeks. Significantly more ADEPT patients achieved clinical success than LRS patients (49% vs 38%). In infertility patients, ADEPT established particular clinical success compared with LRS (55% vs 33%). This was replicated in the number of patients with a reduced American Fertility Society score (53% vs 30%) and in fewer patients with a moderate/severe American Fertility Society category score (43% vs 14%). It showed that ADEPT may be an adjunctive modality in adhesion reduction in laparoscopy [102].

However, another study performed recently could not reproduce similar beneficial effects of this adhesion-preventing entity. The GENEVA study identified a very high incidence of de novo adhesion formation even among facilities specializing in minimally invasive surgery. The investigation found no difference between ADEPT and LRS in overall de novo adhesion formation. These results may advance future adhesion reduction approaches in site-specific surgery such as myomectomy where the use of a site-specific barrier agent, perhaps in conjunction with an instillate solution, may be a better tactic to reduce adhesions [105].

Gore-Tex

Gore-Tex surgical membrane is indicated by the FDA for peritoneal repair and has no effect on coagulation. Gore-Tex requires suturing in place followed by removal after peritoneal healing if desired although the need for removal has been questioned because it is left in place with pericardial or vascular grafts. Expanded polytetrafluoroethylene (ePTFE, Gore-Tex Surgical Membrane) is a nonabsorbable adhesion barrier produced in thin sheets (0.1 mm thick). ePTFE has been approved by the FDA for use in the United States for peritoneal repair. Unlike oxidized regenerated cellulose and hyaluronate film, ePTFE must be sutured to tissue. The product can help to prevent adhesion formation and reformation regardless of the type of injury or whether complete hemostasis has been achieved [45]. In a small randomized trial, ePTFE was found to decrease postmyomectomy adhesions [106]. ePTFE was found to be more effective than oxidized regenerated cellulose in preventing adhesion formation after adnexal surgery in a randomized clinical study. A limitation of the study was that there was no evaluation of adhesions after removal of the membrane barrier [107].

Summary and Conclusions

Postoperative adhesions are a natural consequence of tissue trauma and healing. Adhesiogenesis is a pathological process involving increased ECM production associated with contracted matrix degradation in association with decreased fibrinolytic activity [15]. Investigations have implicated hypoxia is a mediator for the development of the adhesion phenotype by the introduction of inflammatory markers. Cytokines, including interleukin 6 and tumor necrosis factor, stimulate an acute-phase reaction, which leads to a systemic inflammatory response. The inhibition of inflammation may be a possible therapeutic tactic in the preclusion and/or reduction of postoperative adhesion elaboration [93]. It has been postulated that the mechanism by which hypoxia induces the adhesion phenotype is directly through the production of superoxide or through the formation of peroxynitrite suggesting a role for reactive oxygen-free radicals in adhesion formation and the induction of the adhesion phenotype (Binda et al, 2004; Fletcher et al, 2008). In a recent study, a significant reduction in the levels of type I collagen and TGF and VEGF messenger RNAs in response to lycopene and its protective antioxidant effect on the treatment in adhesion fibroblasts compared with normal peritoneal fibroblasts was observed, indicating the potential for altering the wound healing response. ROS activity increases during laparoscopy and laparotomy and appears to be a contributory factor in the pathogenesis of adhesions. Therapies directed at more specific aspects of the pathophysiologic mechanism of the disease including matrix metalloprotease inhibitors, immune modulators, antioxidants, and free radical scavengers may help because they have shown promise in animals [111].

The reduction of postsurgical adhesions remains a medical quandary. A meticulous surgical technique reducing blood loss, minimizing ischemia, and reducing the local inflammatory response may be the most important first step. Avoiding injury to the peritoneum should be paramount in the evaluation of the prevention of adhesions after

intraperitoneal surgery. Influencing the inflammatory response to the peritoneal injury is key in preventing peritoneal adhesions [117]. Every step in the pathophysiology of adhesion formation may be an opportunity to intervene and stop the cascade of events [118]. A better grasp of peritoneal and molecular contrivances involved in adhesion formation will expedite the search for a more simple and effective method. The most common remedy remains to be subsequent adhesiolysis.

Currently, studies involving antiadhesion products should use second-look surgeries with assessment of the development of postoperative adhesions as the primary efficacy end point for trials seeking an indication for adhesion prevention/reduction. Further research is required to develop safe and effective antiadhesion methods in addition to better assessment tools of their efficacy [112]. There is evidence that the use of adhesion barriers in women of reproductive age undergoing conservative surgery in order to conceive will result in a reduction of adhesion development after laparoscopy or laparotomy [54]. Surgeons and their patients should be cognitive of the following postoperative adhesion complications associated with abdominal/pelvic surgery [8]: a high percentage of patients having abdominal/pelvic surgery develop adhesions, the risk of adhesion-related readmission after either laparoscopic or open surgery is comparable [14], and 33% of patients who undergo extensive open surgery are readmitted with adhesion-related complications within 10 years [113]. Seven-five percent of bowel obstructions are caused by postsurgical adhesions [11], and adhesions are responsible for 20% to 40% of secondary infertility cases in women [114].

Postoperative adhesions increase operating times and subsequent challenging surgical procedures that affect risks for bowel injury and have a substantial public health impact. The burden of adhesion-related complications has enormous personal, litigious, and economic costs to patients, physicians, health care expenditures, and society [108,109]. Adhesion development is a significant complication of abdominal and pelvic surgery. The consequences of adhesion development comprise a continuum of potential problems during the life span of the patient. Adhesions can cause significant discomfort, complicate future operative procedures by altering anatomy, increase risk for bowel obstruction, and affect fertility success in women [110]. Its ramifications include billions of dollars of health cost each year because of multiple readmissions to hospitals, surgical interventions, significant decreases in take home babies, and the likelihood of an increase in the frequency of narcotic abuse from chronic pelvic pain. The adequate reduction of postsurgical adhesions and its adverse sequelae continues to elude the scientific community despite a plethora of scientific research in the topic.

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