Pelvic Adhesive Disease: Current Approaches to Management

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Abstract
Pelvic adhesive disease has been identified as a formidable challenge in terms of diagnosis, management and prevention. It accounts for considerable morbidity in the practice of Obstetrics and Gynecology. In the United States, it is estimated that over one billion dollars is spent annually as a result of pelvic adhesive disease and its associated complications. The standard of care regarding current approaches to management and prevention of pelvic adhesive disease continue to be topics of debate. The objective of this article is to provide an overview of the current classification, pathophysiology and approach to the management of pelvic adhesive disease.

Pub Med and Ovid were utilized as search engines. The mesh headings "pelvic adhesions, management, human, female, and pain" were used to review the current literature. Comparison of outcomes from interventions, such as minimally invasive surgery and laporotomy, were addressed. Additionally, uses of FDA (Food and Drug Administration) products designed for adhesion prevention at the time of surgery were reviewed. Controversy still remains how to best manage pelvic adhesions once discovered however it is clear that prevention of adhesions at the time of surgery provides the best outcome.

Keywords
Adhesion prevention; Adhesive disease; Seprafilm; Interceed; Icodextrin

Introduction
Pelvic adhesive disease continues to plague the practice of obstetrics and gynecology, despite advances in surgical technique and work with adhesion prevention adjuvants. The etiology, as well as modalities of diagnosis and approaches to management of pelvic adhesive disease, remains a challenge for physicians and a frustration for patients suffering with the disease. Adhesion development with respect to obstetrics and gynecology is thought to include infection, chemical irritation, prior surgery and endometriosis. Controversy persists regarding the utilities of continuing to manage pelvic adhesive disease by lysis of adhesions surgically, versus alternative medical management of the associated complications of adhesions, such as pelvic pain and infertility. The purpose of this article is to provide an overview of the current literature which addresses the pathophysiology as well as current approaches to management of adhesive disease. Pub Med and Ovid were used as search engines, and pelvic adhesions, management, human, female, and pain was used as mesh headings. The vast majority of multi-center studies examining postoperative adhesion development have been conducted by reproductive endocrinology and infertility sub-specialists. The explanation for this is that assessment and treatment of adhesion development to adnexal structures (which may impair fertility) has potential benefits to the individual, thus justifying the morbidity and possible complications of the second look laparoscopy to assess and treat postoperative adhesions. In this article, we will address the approaches to management which continue to be a topic of debate including whether there is a value to laparoscopic lysis of adhesions versus adhesiolysis at laparotomy.

Classification
Adhesions of the pelvis are defined as non-anatomic connections of fibrous tissue between visceral or parietal peritoneal surfaces at locations at which no connection should exist. Adhesions have been classified as type 1 and type 2 [1]. When assessed at early second-look laparoscopy, Type 1 adhesions are defined as those that develop de novo at a site that did not have adhesions initially, while type 2 develop at a site at which adhesiolysis had been previously performed. Type 1 adhesions can be further subclassified into type 1a, occurring at the site where no previous procedure was performed versus type 1b, where surgical procedures other than adhesiolysis has been performed. Type 2 adhesions can be subclassified into type 2a, adhesions occurring at the site of adhesiolysis only, and 2b, occurring at the site of another procedure with associated adhesiolysis [2]. In a two arm study completed by Menzies et al. in 1990, it was found that of 210 patients undergoing repeat laparotomy, 195 (93%), had adhesions thought to be caused by prior surgery. In the comparison group, of 115 first time laparotomy patients, 12 patients (10.4%) had adhesions [2]. In 1987, Diamond et al. looked at 161 women who underwent laparotomy followed by a second look laparotomy. They found that adhesions developed in 82 (51%) of sites without adhesions at the time of the initial procedure [3]. Evidence thus supports that procedures associated with opening the abdomen are associated with adhesion development and, subsequently, reopening the abdomen in an attempt to remove adhesions may further increase the propensity toward adhesion development.

A clear understanding of the location, type and quantity of adhesions is necessary to achieve a uniform grading system of pelvic adhesions. The one page classification of adnexal adhesions produced by the American Society for Reproductive Medicine remains a commonly used grading system [4]. The classification is composed of three parameters that are measured by the observer. The first parameters look at the severity and consistency of the adhesion; whether filmy or dense. The second parameter looks at the site of the adhesion; whether on the fallopian tube or ovary. Additionally, the side of the adhesion (right and/or left) is documented at that time. Lastly, the extent of the adhesion at that location is quantified to whether less than one third, one third to two-thirds, or greater than two-thirds of the entire organ is involved with adhesions. Once the scores are compiled, the overall adhesive disease is categorized as minimal (score 0-5), mild (score 6-10), moderate (score 11-20) or severe (score 21-32) [4]. Although the American Fertility Society Classification of Adnexal Adhesions form allows for standardization of adhesion types and location, there have been no prospective studies in the literature to correlate findings and score with prognosis. Additionally, though this system has been used extensively throughout the years to grade...
In the context of pelvic adhesions, it is crucial to consider both the adhesion consequences of laparoscopic and laparotomy surgical approaches. The pathophysiology of adhesions is a complex process involving factors such as trauma, devascularization, and the activation of inflammatory and angiogenic pathways.

**Pathophysiology**

Over the past several decades, the pathophysiology of adhesion formation has been studied at macroscopic, microscopic, and molecular levels. Adhesions develop as a response to injury of peritoneal tissue. The serosal membrane of the peritoneal surfaces is lined by mesothelial cells loosely attached to a basement membrane. Once injury occurs to the mesothelial cells, whether as a consequence of trauma or devascularization such as with incision, fulguration of trauma or devascularization such as with incision, fulguration or ligation of the tissue, a cascade of events is initiated. Mast cells release vaso-active substances including histamines and kinins. These substances contribute to vascular permeability with subsequent elaboration of a fibrin-rich exudate that covers the injured area. The fibrin exudate interacts with fibronectin and other forms of extracellular matrix forming a gel from which fibrin bands develop between the injured areas. Fibrinolysis also occurs at these areas by the conversion of plasminogen to plasmin by tissue plasminogen activator (tPA). If sufficient plasminogen activator activity persists, the fibrinous mass invades the area and deposit extracellular matrix material, including collagen, which contributes to the adhesion development. Ischemia plays a significant role in the propensity for adhesion development, as it has been shown that fibroblasts in ischemic tissue manifest a different phenotype than do those in non-ischemic tissue. Additionally, hypoxia has been shown to convert normal phenotype fibroblasts to different phenotype fibroblasts (e.g. myofibroblast) [1]. COX-2 enzyme, which has shown to be a significant factor in the regulation of inflammation and angiogenesis in adhesion development, is also noted to be significantly increased in the phenotypically transformed adhesion myofibroblasts, as compared to normal peritoneal fibroblasts [5].

**Management**

As technology advances, the role of minimally-invasive surgical techniques such as laparoscopy in the management of pelvic adhesions has reached new prominence. However, it is prudent to consider both the adhesion consequences of laparoscopic and laparotomy surgical approaches. It has been stated in the literature that the rate of adhesion development after gynecologic surgery is between 55 and 100 percent, regardless of the method of surgical approach [6]. A randomized perspective human study, done by Luandorff et al., examined the development of adhesions in 105 patients treated for tubal ectopic pregnancy. The patients were randomized to either laparotomy or laparoscopic intervention. It was discovered that there was reduced adhesion development in the laparoscopic group compared to the laparotomy group at second look laparoscopy. However, the difference was not statistically significant [7]. Additionally, when clinicians examined adhesion development after ovarian endometrioma resection, it was found that adhesions were less frequent in laparoscopy patients (37.2 percent) as opposed to laparotomy (54.2 percent) [8]. (Figure 1) A prospective, multicenter study conducted by The Operative Laparoscopy Study Group looked at 68 patients who had operative laparoscopy including adhesiolysis followed by second look laparoscopy procedure within 90 days of an initial laparoscopic surgical procedure. They noted that there was a significant reduction in adhesions (52% in total mean adhesions score), however, 97 percent of the patients had some type of adhesion development [6]. Additionally, 12% of patients had de novo adhesion formation and 66% of patients had adhesion reformation at previously lysed adhesions sites [6]. (Figure 2) After a review of the literature, it can be concluded that adhesion development is common in both laparotomy and laparoscopy, however there is no consistently demonstrated benefit of laparoscopy for a reduced risk of adhesion formation compared to laparotomy [6,9,10].

The benefit of closure of the visceral or parietal peritoneal surface, as it relates to subsequent adhesion development, is also controversial. Kadanalin, et al. looked at peritoneal and non-peritoneal closure at lymphadenectomy with ovarian cancer. On second look laparotomy, the adhesion scores were lower when the pelvic peritoneum was not closed [11]. However Lyell, et al. conducted a prospective cohort study of women undergoing first repeat cesarean deliveries. One hundred and seventy-three patients were enrolled in the study. Exclusion criteria included adhesions, previous surgery, use of peritoneal suture at time of cesarean, unavailable first c-section operative note, wound infection or breakdown following surgery, intervening pelvic surgery, insulin-dependent diabetes and/or steroid dependent disease. They found that parietal peritoneal closure was associated with significantly fewer dense and filmy adhesions (P=0.006) and significantly fewer dense adhesions (P=0.043) [12]. In another study, Lyell, et al. performed a secondary analysis of the
distending medium used in hysteroscopy because it is electrolyte free, in the peritoneal cavity. Solutions such as 32 percent dextran 70, a Solution have not demonstrated any decrease in adhesion formation Crystalloid solutions such as normal saline and Lactated Ringers of absorption by the peritoneum, approximately 100 mL an hour. As prevention remains good surgical techniques, including un-

There is no one specific measure found to completely prevent adhesion development in all patients. Over the years, there have been several new interventions that have shown to have some effectiveness in reducing adhesion formation, both de novo and recurrent, following both laparotomy and laparoscopic surgical approaches. The fundamental approach to post-surgical adhesion prevention remains good surgical techniques, including un-

nonconducting, biodegradable, and optically clear, have been shown to have variable efficiency in reducing adhesion development, but have been associated with abdominal bloating and vulva and lower extremity edema. Icodextrin 4% solution (Adept, Baxter Healthcare Corp.) was evaluated in a multicenter, prospective, randomized, double blind study comparing it with Lactated Ringers Solution (LRS). Icodextrin 4% solution functions as a colloid osmotic agent that retains fluid within the peritoneal cavity for an interval of 3 to 4 days. In the study by Brown, et al., 402 patients undergoing laparoscopic gynecologic surgery for adhesiolsy were randomized intraoperatively to receive Adept (203 patients) or LRS (199 patients) to be left in the peritoneal cavity to separate damaged peritoneal surfaces and prevent contact between organs during the time of postoperative repair by a process termed as hydrofloation. Patients

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Manufacturer</th>
<th>Action</th>
<th>Where used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Icodextrin 4% solution*</td>
<td>Adept solution (Baxter Healthcare Corp.)</td>
<td>Colloid osmotic agent that retains fluid within the peritoneal cavity to separate damaged peritoneal surfaces and prevent contact between organs during the time of postoperative repair by a process termed hydrofloation.</td>
<td>Laparoscopy</td>
</tr>
<tr>
<td>Modified hyaluronate and carboxymethylcellulose compound*</td>
<td>Seroplatin (Genzyme Corp.)</td>
<td>Cover denuded and raw surfaces of tissue</td>
<td>Laparotomy</td>
</tr>
<tr>
<td>Oxidized Regenerated Cellulose*</td>
<td>Interceed (Johnson &amp; Johnson Medical)</td>
<td>Forms a gel and physically separates tissue layers during tissue healing. Additionally, has been shown to alter the inflammatory response by managing macrophage immunologic response and subsequent decrease adhesion formation</td>
<td>Laparotomy</td>
</tr>
<tr>
<td>Normal Saline and Lactated Ringers</td>
<td></td>
<td>Theoretically, the process termed hydrofloation is when the solution is left in the peritoneal cavity to separate damaged peritoneal surfaces and prevent contact between organs during the time of postoperative repair</td>
<td>No study has demonstrated any decrease in adhesion formation in the peritoneal cavity</td>
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*Product is FDA approved for adhesion prevention in the United States.

prospective cohort study. This study looked at adhesions in women who underwent first repeat cesarean delivery and the effects of the closure of the rectus muscle and visceral peritoneum at cesarean delivery [13]. Visceral peritoneal closure was associated with an increased dense fascia to omentum adhesion with an OR of 15.78 and a 95% CI. Rectus muscle closure was associated with fewer combined filmy and dense adhesions (P=0.04) and dense adhesions (P=0.001) in women who underwent first repeat cesarean delivery [13]. The study followed 45 patients that were randomized to peritoneal closure and nonclosure. The adhesion score of the patients having their second cesarean section were evaluated and the nonclosure group had 7 patients (54%, P=0.05) that developed adhesions of which 2 had severe adhesions. In the closure group, 3 patients (15%, P=0.05) had developed adhesions that were mild in nature (easily removable). In contrast, Tulandi, et al. did a review of the literature to evaluate the advantages and disadvantages of nonclosure of the peritoneum. They cited several different studies, including their study in 1988 where they examined at adhesion formation in gynecologic operations after parietal peritoneal closure as assessed by a second look laparoscopy. They reported no significant difference in adhesion formation after laparotomy with peritoneal closure (22.2%) or without peritoneal closure (16%) [14]. Thus, there are confounding results on the value of closure of the parietal and visceral peritoneum.

**Prevention**

There is no one specific measure found to completely prevent adhesion development in all patients. Over the years, there have been several new interventions that have shown to have some effectiveness in reducing adhesion formation, both de novo and recurrent, following both laparotomy and laparoscopic surgical approaches. The fundamental approach to post-surgical adhesion prevention remains good surgical techniques, including unpowdered gloves and minimal tissue injury devascularization. As early as 1886, it was thought that leaving crystalloid solutions in the abdomen after surgery would prevent adhesion formation in the postsurgical patient. This was perhaps in part due to the rapid rate of absorption by the peritoneum, approximately 100 mL an hour. Crystalloid solutions such as normal saline and Lactated Ringers Solution have not demonstrated any decrease in adhesion formation in the peritoneal cavity. Solutions such as 32 percent dextran 70, a distending medium used in hysteroscopy because it is electrolyte free,
study involving 183 patients with ulcerative colitis looked at the incidence, extent, and severity of adhesion development to the midline incision as assessed at an 8-12 week second look laparoscopy following Seprafilm placement under the midline incision just before abdominal closure. They found that 51% of the patients who had Seprafilm placed had no adhesions at the incision line whereas only 6% of the non-Seprafilm patients were adhesion free at the incision line (P<0.001) [19]. It is important to note that The Food and Drug Administration (FDA) approval for Interceed and Seprafilm is only indicated for open procedures. They do not have an indication for laparoscopic procedures. There is currently a common practice of using what is called a "shroud", which is a mixture of saline and crushed-up Seprafilm used at the conclusion of gynecologic laparoscopic procedures. Although this may seem plausible, such alteration of Seprafilm is a non-approved use of this product, and may alter the desired effect. There are currently no prospective randomized controlled studies on this mixture and therefore further evaluation needs to be done prior to recommending it as an adhesive barrier.

Conclusion

The management of adhesive disease and its sequelae remains of great importance to the gynecologic care of women. It is estimated that adhesive disease and its associated complications account for approximately $1 billion per year in the United States [20-22]. The pathophysiology of adhesive disease has been studied and we are now aware of the potential sources of adhesion development. We are also aware that continued surgery for adhesive disease could "feed" into the cycle of further adhesion development. There is extensive literature on the surgical approach to minimize adhesions development. It appears that although both laparotomy and laparoscopy are associated with adhesion development, there is no consistent evidence of fewer adhesions formed in laparoscopic surgery than in laparotomy. The surgical duration can be a confounding factor as prolonged exposure to CO₂ may irritate the peritoneum; additionally, fulguration and devascularization of the tissue during laparoscopic surgery may promote adhesion development. There is much debate in the literature as to whether or not to close the parietal peritoneum in both obstetrical and gynecological procedures. There are currently several adhesion prevention products approved by the FDA for management and prevention of adhesive disease following gynecologic procedures.

Closure of the peritoneum at the time of surgery, however, is controversial. Based on what has been previously elucidated regarding the physiologic development of adhesive disease, we do not know whether irrigation, ensuring hemostasis and minimizing trauma to the peritoneal and surrounding surfaces will contribute to decreasing the risk of adhesion development. Products such as Intercede and Seprafilm have been extensively used and studied for adhesion prevention in open gynecologic surgical procedures. Products that can be used following laparoscopic surgery need to be further evaluated. Although a great deal of research has been conducted to date to assist in the management and prevention of adhesion development, we must continue to evaluate efficacy of our current management approaches and remain diligent in elucidating innovative interventions that have the potential to successfully be employed in the treatment and prevention of the development of pelvic adhesive disease.

References