

# Preventing Adhesions in Obstetric and Gynecologic Surgical Procedures

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*Adhesive disease represents a significant cause of morbidity for postoperative patients. Most surgical procedures performed by obstetrician-gynecologists are associated with pelvic adhesions that cause subsequent serious sequelae, including small bowel obstruction, infertility, chronic pelvic pain, and difficulty in postoperative treatment, including complexity during subsequent surgical procedures. The technology of adhesion prevention has significantly progressed. There are 3 methods approved by the US Food and Drug Administration for the prevention of postoperative adhesions, including Adept®, Interceed®, and Seprafilm®. The latter barrier is the most widely studied. This article reviews the current choices available for adhesion prevention barriers as well as surgical adjuncts that traditionally have been studied for that purpose.*

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Obstetricians-gynecologists (ob-gyns) perform 2 of the most common surgical procedures in the United States: cesarean delivery and abdominal hysterectomy. These procedures, as well as others (such as myomectomy, ovarian cystectomy, and surgeries for invasive gynecologic malignancies), are associated with a risk of developing pelvic adhesions, with their associated morbidity. More than 400,000 surgical procedures are performed daily in the United States for lysis of adhesions, with the economic impact exceeding \$1.3 billion per annum.<sup>1</sup> The burden of adhesion formation has therefore become a growing concern, and its prevention should be a priority. This article reviews the adjunctive methods available for the ob-gyn to prevent postoperative adhesion formation.

### Adhesion Formation

Adhesion formation begins immediately after surgery. Following tissue trauma, inflammation brings macrophages, fibroblasts, and a fibrin matrix to the surface of the wound (Figure 1). On approximately day 3 after surgery, macrophages form the foundation of the advancing adhesion. Fibrin matrix advancement occurs with the proliferation of fibroblasts and vascularization. By day 5, the advancing adhesions are increasingly vascular and organized in structure. No new

adhesion formation occurs after day 7.<sup>2</sup> Theoretically, optimal prevention of adhesion formation requires interven-

or treatment related. Physical morbidity includes small bowel obstruction (SBO), infertility, chronic pain, and

*Optimal prevention of adhesion formation requires intervention throughout the critical 7-day period of peritoneal healing.*

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### Adhesion-Related Morbidity

Adhesion-related morbidity can be divided into 2 main categories: physical

dyspareunia. Treatment-related morbidity includes difficulty with post-operative interventions such as intraperitoneal chemotherapy, radiation, and subsequent complications during repeat operations.

### Small Bowel Obstruction

Adhesions have been implicated as the cause of 54% to 74% of all cases of SBO.<sup>3</sup> Indeed, SBO requiring surgery has been associated most commonly with adhesions in the pelvis or to prior surgery.<sup>4</sup> Beck and colleagues<sup>5</sup> estimated that 1 in 6 colorectal surgery patients are readmitted for SBO within 2 years of their original surgery. Up to 56% of women with adhesion-related SBO have had at least 1 previous pelvic procedure, most commonly hysterectomy.<sup>6</sup> Extensive gynecologic surgeries for malignancy coupled with radiation therapy further increase the risk of developing SBO. Montz and colleagues<sup>7</sup> published data on the incidence of SBO after radical hysterectomy. Among the 98 patients included in the study, SBO was reported in 5% of patients not receiving radiotherapy, in 20% of those receiving radiotherapy following surgery, and in 22% of patients receiving radiotherapy prior to surgery. Of all women who developed SBO, 54% required surgical management.

### Infertility

Intra-abdominal adhesive disease is associated with up to 15% to 20% of all cases of infertility.<sup>8</sup> Although its causal association with infertility has not been definitively established,

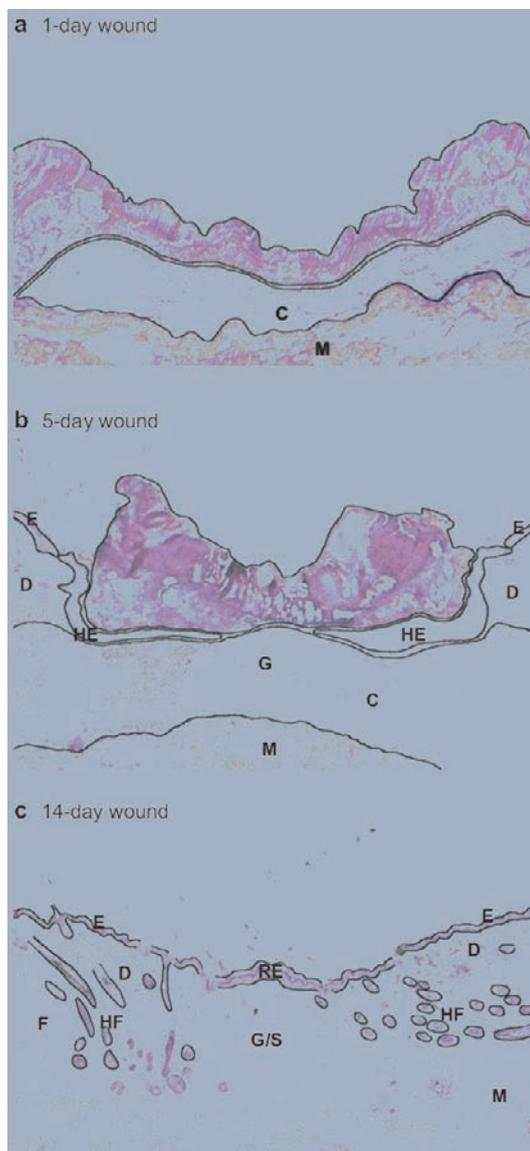


Figure 1. Different stages of the wound healing process. Full-thickness excisional mouse wounds are shown at (a) day 1 (inflammatory phase), (b) day 5 (phase of new tissue formation), and (c) day 14 (phase of tissue remodeling). The different components of the healing skin wounds are indicated. C, clot; D, dermis; E, epidermis; ES, eschar; F, fatty tissue; G, granulation tissue; HE, hyperproliferative epithelium; HF, hair follicle; M, muscle; RE, regenerating epithelium; G/S, late granulation tissue/early scar tissue. Reprinted, with permission, from *Annual Review of Cell and Developmental Biology*, Volume 23, © 2007 by Annual Reviews. [www.annualreviews.org](http://www.annualreviews.org).

pelvic adhesions are thought to restrict the free movement of pelvic organs.

#### *Chronic Pelvic Pain*

Chronic pelvic pain is a major gynecologic problem, accounting for 10% of all gynecologic visits and approximately 50% of laparoscopic investigations.<sup>9</sup> Adhesive disease has been estimated to account for up to 50% of all cases of pelvic pain. The mechanism may be similar to that proposed in women with infertility, with restriction of the free movement of the pelvic organs.

#### *Postoperative Considerations*

Adhesive disease diminishes the efficacy of intraperitoneal chemotherapy by preventing its even distribution throughout the abdominopelvic cavity. Adhesions limit the free movement of the bowel, which can lead to radiation-induced enteritis secondary to postoperative radiation therapy. Adhesions have also been associated with an increased risk of surgical complications during subsequent operations. These include, among others, inadvertent enterotomy, postoperative complications such as bowel leaks and wound dehiscence, and an increase in length of postoperative hospital stay.<sup>10</sup>

#### **Prevention of Postoperative Adhesions**

It is clear that adhesive disease is a major cause of serious morbidity among women undergoing surgical procedures. As such, adhesion prevention has become an area of interest for many practitioners. Traditionally, good surgical technique was advocated as the main way to prevent postoperative adhesions. This included strict adherence to the basic surgical principles of minimizing tissue trauma with meticulous hemostasis, minimization of ischemia and desiccation, and prevention of infec-

tion and foreign body retention. Peritoneal closure deserves separate discussion because much debate has occurred in the medical literature with inconclusive results, particularly within the discipline of obstetrics-gynecology. Historically, peritoneal closure has been performed to reduce postoperative complications, including adhesions. Review of the literature does not support the closure of peritoneum to prevent adhesions.<sup>11</sup>

Other surgical adjuncts to prevent adhesion formation include irrigation with crystalloid solutions, high-molecular-weight dextran, heparin, and administrations of nonsteroidal anti-inflammatory drugs (NSAIDs). The use of crystalloid solutions is known as *hydroflotation*; some crystalloid is left in the pelvis at the end of surgery to allow the tissues to float apart from one another and thereby decrease the risk of adhesion formation. Results from multiple studies looking at the use of hydroflotation with crystalloids have been discouraging. For example, results of a meta-analysis of 259 reports from 1966 through 1996 concluded that crystalloid does not reduce adhesion formation, and the authors suggested that its use be discouraged.<sup>12</sup> Other investigators add heparin to the crystalloid solutions used for irrigation. The rationale behind the use of heparin includes the prevention of blood clotting and fibrin deposition, which are involved in adhesion formation. Unfortunately, the largest randomized, placebo-controlled clinical trial addressing this approach showed no benefit in terms of adhesion formation between the study and control groups.<sup>13</sup>

High-molecular-weight dextran has also been used for hydroflotation. Due to its high viscosity and long half-life in the peritoneal cavity, concerns have arisen about excessive fluid shifts leading to cardiovascular compromise.

However, results of prospective randomized trials evaluating the efficacy of high-molecular-weight dextran are conflicting.<sup>14</sup>

NSAIDs have also been recommended to prevent postoperative pelvic adhesions by blocking the production of thromboxanes, which are known to be involved in the biochemical pathways leading to adhesion formation. However, lack of adequate studies evaluating their safety and efficacy has limited their clinical application.

Adept® Adhesion Reduction Solution (Innovata plc, Surrey, UK) has been recently added to the armamentarium of adhesion prevention as an adjunct used intraperitoneally in patients undergoing gynecologic laparoscopic adhesiolysis. Adept is a 4% icodextrin solution made of an  $\alpha(1-4)$ -linked glucose polymer that acts via hydroflotation. However, its efficacy appears to be limited, as evidenced in a pivotal clinical trial that showed only marginal superiority over lactated Ringer's solution in the prevention of postoperative adhesions.<sup>15</sup> In the same trial, a number of treatment-related complications were identified, including excessive edema of the labia, vulva, and vagina.

#### **Use of Adhesion Barriers**

The ideal adhesion barrier should meet the following criteria: (1) achieves effective tissue separation; (2) has a long half-life within the peritoneal cavity so that it can remain active during the critical 7-day peritoneal healing period; (3) is absorbed or metabolized without initiating a marked proinflammatory tissue response; (4) remains active and effective in the presence of blood; (5) does not compromise wound healing; and (6) does not promote bacterial growth. Current adhesion barriers include expanded polytetrafluorethylene (Gore-Tex® surgical membrane; W. L. Gore &

Associates, Inc., Flagstaff, AZ) and the 2 FDA-approved barriers: oxidized regenerated cellulose (Interceed®; Ethicon Endo-Surgery, Somerville, NJ) and sodium hyaluronate and carboxymethylcellulose (Seprafilm®; Genzyme Corporation, Cambridge, MA).

#### *Expanded Polytetrafluoroethylene (Gore-Tex Surgical Membrane)*

Expanded polytetrafluoroethylene has a microscopic structure preventing cellular growth. It is noninflammatory and nonabsorbable. It does not adhere to tissue and must be sutured in place. Data on clinical efficacy exist, but are limited. In a trial of 27 women, the Myomectomy Adhesion Multicenter Study Group reported a significant reduction in adhesion formation to the uterine surface following Gore-Tex application as compared with controls.<sup>16</sup> In another clinical trial, Haney and colleagues<sup>17</sup> reported an 85% reduction in adhesion formation with Gore-Tex compared with 65% with Interceed. In a prospective, multicenter, observational trial, Hurst<sup>18</sup> reported on the long-term follow-up of patients who received Gore-Tex barriers. There was a single case of postoperative infection that did not necessitate removal of the membrane, and all other patients did well. These data suggest that the membrane can probably be left in place indefinitely.

#### *Oxidized Regenerated Cellulose (Interceed)*

The adhesion barrier, Interceed, is made of oxidized regenerated cellulose and is available in 3" × 4" sheets. The efficacy of Interceed has been studied in more than 13 clinical studies that included over 600 patients. A meta-analysis of 10 randomized, controlled studies reported a 24.2% reduction in adhesion formation on the side treated with Inter-

ceed, compared with the control side.<sup>19</sup> Despite this report, concerns about Interceed continue, especially regarding its efficacy in preventing adhesions and its apparent ineffectiveness in the presence of blood. In this setting, Interceed may aggravate rather than prevent adhesion formation. The safety and effectiveness of Interceed in preventing adhesion formation in laparoscopic surgery or any procedures other than open gynecologic microsurgical procedures have not been established.

#### *Sodium Hyaluronate and Carboxymethylcellulose (Seprafilm)*

Seprafilm is perhaps the most widely studied adhesion barrier, with more than 20 published studies that included over 4600 patients. Seprafilm is composed of chemically modified hyaluronic acid and carboxymethylcellulose. It is designed to separate planes of tissues after surgery for 3 to 7 days. To date, there is no evidence that Seprafilm is adhesiogenic in the presence of blood. The clinical trials reporting on the use of Seprafilm to prevent adhesion formation are summarized in Table 1, including population demographics, study design, sample size, and a brief summary of the results.

Writing for the Seprafilm Adhesion Study Group, Diamond<sup>20</sup> reported on the safety and efficacy of Seprafilm in preventing postoperative uterine adhesions after myomectomy. This was a prospective, double-blind, multicenter, randomized, controlled study. After surgical treatment with or without Seprafilm, all patients were evaluated by early, second-look laparoscopy for the incidence, severity, and extent of adhesions. This study also evaluated the number of adhesion sites throughout the pelvis and the area of adhesions. In patients undergoing myomectomy, Seprafilm re-

duced the incidence, severity, extent, and average surface area of uterine adhesions. Approximately 48% of patients randomized to Seprafilm had at least 1 adnexa free of adhesions, and there was no increased risk of complications such as ileus, intra-abdominal bleeding, and postoperative fever.<sup>20</sup> Bristow and Montz<sup>21</sup> studied the effectiveness of Seprafilm in preventing pelvic adhesions in women undergoing primary cytoreductive surgery with radical oophorectomy. In this cohort, Seprafilm significantly reduced the mean adhesion score by 84% compared with the internal controls and by 90% compared with historical control groups. The authors concluded that 73.2% of Seprafilm placement sites were free of adhesions compared with 35.7% for the abdominal wall and 14.3% for untreated pelvis. Moreover, in those Seprafilm placement sites that did have adhesions, the adhesions were significantly less severe than untreated sites. No complications were attributed to the presence of Seprafilm.

The economic impact of adhesions and the cost effectiveness of Seprafilm treatment were studied by the same investigators. By creating a theoretical decision model, they concluded that Seprafilm use offers an incremental savings of \$383 (payers) and \$1122 (society) per patient over a 10-year period. They concluded that the use of Seprafilm was cost effective with a threshold of \$1571 (7 sheets).<sup>22</sup>

Concerns about the use of Seprafilm include the learning curve required to achieve optimal placement and the fact that it cannot be applied laparoscopically.

#### **Adhesion Prevention at the Time of Cesarean Delivery**

Cesarean deliveries and adhesive disease deserve separate discussion. With the rise in cesarean delivery rates and

Table 1  
Seprafilm Clinical Overview

Study and Population	Trial Design and Sample Size	Brief Summary of Results
Becker et al. ( <i>Am Coll Surg.</i> 1996;183:297-306) Colectomy w/IPPA	Randomized, controlled trial N = 183	Seprafilm was reported to be safe and effective in reducing adhesion formation to the midline incision
Beck et al. ( <i>Dis Colon Rectum.</i> 2003; 46:1310-1319) Colorectal resection	Randomized, controlled trial N = 1791	Seprafilm was reported to be safe when used as directed, and to significantly reduce adhesive small bowel obstruction requiring reoperation during a mean follow-up of 3.5 years
Mohri et al. ( <i>Am Surg.</i> 2005;71:861-863) Gastrointestinal surgeries	Retrospective analysis N = 367	Seprafilm was reported to significantly lower the incidence of early postoperative bowel obstruction when compared with matched controls undergoing abdominal surgery; surgical site infection rates were similar in both groups
Park et al. ( <i>Int J Colorectal Dis.</i> 2009;24:305-310) Colorectal resection Colorectal cancer	Prospective, randomized, controlled trial N = 427	The incidence of early postoperative bowel obstruction was significantly less in the Seprafilm group versus the control group; no differences in reported adverse events
Vrijland et al. ( <i>Ann Surg.</i> 2002;235:193-199) Hartmann procedure	Randomized, controlled trial N = 71	Seprafilm was reported to be safe and to significantly reduce the severity of adhesions to the midline incision and in the pelvis
Tang et al. ( <i>Dis Colon Rectum.</i> 2003;46:1200-1207) Rectal resection	Randomized, controlled trial N = 175	Seprafilm was reported to reduce overall mean peristomal adhesion scores and allowed for easier closure of the stoma
Oikonomakis et al. ( <i>Dis Colon Rectum.</i> 2002;45:1376-1380) Radical colorectal surgery	Retrospective study N = 156	Seprafilm was reported to not adversely affect the short-term recurrence rate; 1- and 2-year survival rates were equivalent
Kusunoki et al. ( <i>Surg Today.</i> 2005;35:940-945) Radical rectal resection	Randomized, controlled trial N = 62	Seprafilm was reported to reduce adhesions to the midline and stoma and had no adverse effect on oncologic outcome
Uchida et al. ( <i>Surg Today.</i> 2005;35:1054-1059) Bowel resection	Cohort study N = 278	Seprafilm was reported not to increase the rate of postoperative inflammatory response or septic conditions following radical surgery for rectal cancer
Bristow & Montz ( <i>Gynecol Oncol.</i> 2005;99:301-308) Radical ovarian surgery	Prospective, controlled study N = 14	Seprafilm was reported to significantly decrease the mean adhesion scores in treated pelvic areas vs the patients' own untreated abdominal wall or the untreated pelvic areas of 7 historical controls; there were no reports of complications related to Seprafilm
Tan et al. ( <i>Ann Surg Oncol.</i> 2009;16:499-505) Gynecologic malignancies	Retrospective study N = 202	HA-CMC does not affect disease-free or overall survival, nor does it increase postoperative complication rates in patients undergoing abdominal surgery for ovarian, fallopian tube, and primary peritoneal carcinomas
Diamond et al. ( <i>Fertil Steril.</i> 1996;66:904-910) Uterine myomectomy	Randomized, controlled trial N = 127	Seprafilm was reported to be safe and effective in reducing postoperative adhesion formation to application sites in the pelvis

(Continued)

Table 1  
(Continued)

Study and Population	Trial Design and Sample Size	Brief Summary of Results
Salum et al. ( <i>Dis Colon Rectum</i> . 2001;44:706-712) Colorectal surgeries	Cohort study N = 438	Seprafilm was reported to show a trend in reducing the incidence of small bowel obstruction and enterolysis for obstruction; the morbidity and mortality rates and the incidence of overall and abdominopelvic septic complications were similar to an untreated control group
Inoue et al. ( <i>J Pediatr Surg</i> . 2005;40:1301-1306) Pediatric abdominal	Cohort study N = 122	Seprafilm was reported to safely and effectively reduce the incidence and severity of adhesions under the midline incision
Fushiki et al. ( <i>Obstet Gynecol Treat</i> . 2005;91:557-561) Cesarean delivery	Cohort study N = 52	Seprafilm was reported to significantly reduce the time to delivery, surgery time, and adhesions in patients undergoing repeat cesarean delivery

HA-CMC, hyaluronate-carboxymethylcellulose; IPPA, ileal pouch-anal anastomosis.

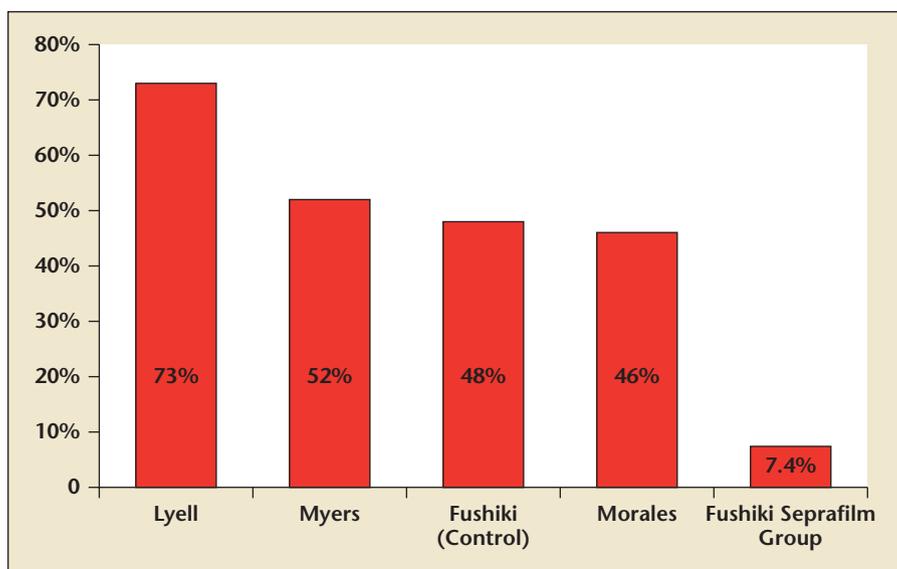
the decline in rates of vaginal birth after cesarean worldwide, ob-gyns should expect to see a rise in complications due to adhesive disease during repeat cesarean deliveries. Figure 2 describes the incidence of adhesions following primary cesarean delivery in the published literature, which ranges from 46% to 65%.

Morales and colleagues<sup>23</sup> performed a retrospective study to describe the

incidence of adhesions after cesarean delivery. They reported on the severity and location of adhesions, delivery time, cord blood pH, and Apgar score. The incidence and severity of adhesions after cesarean delivery increased significantly with each subsequent delivery. As expected, the incision-to-delivery time correlated directly with the presence and severity of adhesions (Figure 3).

The data on adhesion prevention at the time of cesarean delivery are limited to a single study. Fushiki and colleagues<sup>24</sup> performed a prospective cohort study of Seprafilm placement at the time of primary cesarean delivery with a view to reducing adhesive disease. In all instances, the presence and severity of adhesions was evaluated at the time of 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%, respectively;  $P = .001$ ; and an adhesion score of 0.07 vs 1.32, respectively;  $P = .001$ ). The same study indicated a statistically significant decrease in time to delivery. Figure 4 depicts the application of Seprafilm.

Figure 2. Incidence of adhesions at first repeat cesarean delivery.



### Summary

Despite significant progress in the development of adhesion prevention barriers, adhesive disease continues to be a major cause of morbidity in postoperative patients with both short- and long-term sequelae. Ob-gyns should keep up to date with data concerning adhesion prevention, and

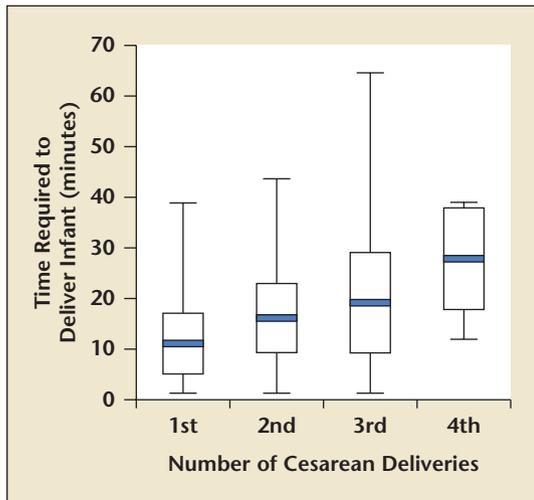


Figure 3. Delayed infant delivery and number of cesarean deliveries. Reprinted with permission from Morales KJ et al.<sup>23</sup>

active for at least 5 to 7 days, its ability to be absorbed, and the inert metabolic products that need to be excreted. For procedures such as myomectomies and cesarean deliveries where blood loss and contamination of the operative field is inevitable, the practitioner should be aware of the effect of blood or inflammation on the adhesion prevention barrier. ■

*Dr. González-Quintero has disclosed affiliation with Genzyme. Dr. Cruz-Pachano has no disclosures to report.*

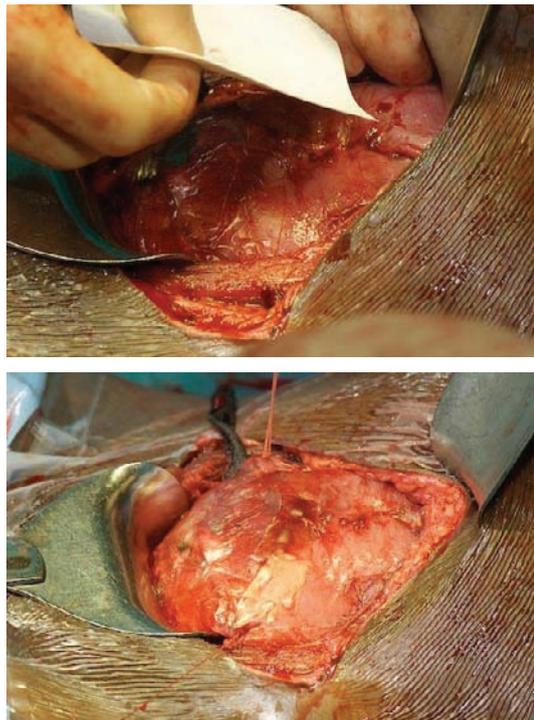


Figure 4. The application of Seprafilm® (Genzyme Corporation, Cambridge, MA) during cesarean delivery.

make reasonable and informed decisions about whether to use such techniques in their individual practices. When selecting the most appropriate

adhesion barrier, the practitioner should take into consideration the half-life of the barrier in the abdomen to ensure that it remains biologically

*When selecting the most appropriate adhesion barrier, the practitioner should take into consideration the half-life of the barrier in the abdomen to ensure that it remains biologically active for at least 5 to 7 days, its ability to be absorbed, and the inert metabolic products that need to be excreted.*

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## Main Points

- More than 400,000 surgical procedures are performed daily in the United States for lysis of adhesions, with the economic impact exceeding \$1.3 billion per annum.
- Physical adhesion morbidity includes small bowel obstruction, infertility, chronic pain, and dyspareunia. Treatment-related adhesion morbidity includes difficulty with postoperative interventions such as intraperitoneal chemotherapy, radiation, and subsequent complications during repeat operations.
- Good surgical technique was advocated as the main way to prevent postoperative adhesions. This included strict adherence to the basic surgical principles of minimizing tissue trauma with meticulous hemostasis, minimization of ischemia and desiccation, and prevention of infection and foreign body retention.
- The ideal adhesion barrier should meet the following criteria: (1) achieves effective tissue separation; (2) has a long half-life within the peritoneal cavity so that it can remain active during the critical 7-day peritoneal healing period; (3) is absorbed or metabolized without initiating a marked proinflammatory tissue response; (4) remains active and effective in the presence of blood; (5) does not compromise wound healing; and (6) does not promote bacterial growth.