Adhesion formation after intracapsular myomectomy with or without adhesion barrier

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Objective: To show the prevention of adhesion formation by placing an absorbable adhesion barrier after intracapsular myomectomy.
Design: Prospective blinded observational study.
Setting: University-affiliated Hospitals.
Patient(s): Patients ≥18 years old with single or multiple uterine fibroids removed by laparoscopic or abdominal intracapsular myomectomy.
Intervention(s): A total of 694 women undergoing laparoscopic or abdominal myomectomy were randomized for placement of oxidized regenerated cellulose absorbable adhesion barrier to the uterine incision or for control subjects without barriers. The presence of adhesions was assessed in 546 patients who underwent subsequent surgery.
Main Outcome Measure(s): The primary and secondary outcomes of the analysis were the presence and severity of adhesions for four groups: laparotomy with barrier, laparotomy without barrier, laparoscopy with barrier, and laparoscopy without barrier.
Result(s): There was a higher rate of adhesions in laparotomy without barrier (28.1%) compared with laparoscopy with no barrier (22.6%), followed by laparotomy with barrier (22%) and laparoscopy with barrier (15.9%). Additionally, the type of adhesions were different, filmy and organized were predominant with an adhesion barrier, and cohesive adhesions were more common without an adhesion barrier.
Conclusion(s): Oxidized regenerated cellulose reduces postsurgical adhesions. Cohesive adhesions reduction was noted in laparoscopy. (Fertil Steril® 2011;95:1780–5. ©2011 by American Society for Reproductive Medicine.)

Key Words: Adhesion, intracapsular myomectomy, laparoscopy, uterine leyomyoma, fibroid, adhesion prevention, Interceed, oxidized regenerated cellulose, fertility, pelvic pain, adhesiolysis

Postoperative adhesions of pelvic or abdominal surgery is a known complication (1). Adhesions may include bowel obstruction, chronic pelvic pain, and infertility in women (2, 3). An absorbable barrier composed of oxidized regenerated cellulose (ORC; Interceed, Johnson & Johnson, New Brunswick, NJ), has been shown to reduce adhesion formation (4) in both animal models (5–7) and human clinical trials (8, 9). This adhesion barrier is placed on the surgical site. It helps to prevent postoperative adhesions by protecting and separating the surfaces of denuded peritoneum where adhesions are likely to form, and it dissolves as healing occurs. ORC increases the tissue plasminogen activator (tPA)/plasminogen activator inhibitor (PAI) 1 ratio in fibroblasts isolated from adhesion tissues (10) and reduces the inflammatory response by acting on macrophages, another potential mechanism to decrease adhesion formation (11). One study reported that 55%–97% of women undergoing pelvic surgery form adhesions; several investigators reported that adhesions after myomectomy by laparotomy occurred in all patients (12). Currently, laparoscopy is commonly used in myomectomies. ORC was used in laparoscopic myomectomy trials with beneficial results (13, 14). The present prospective randomized study was conducted to determine if ORC reduces the risk of adhesions after laparoscopic as well as abdominal intracapsular myomectomy (15, 16).

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MATERIALS AND METHODS

Six hundred ninety-four women ≥18 years old underwent laparoscopic or abdominal single or multiple intracapsular myomectomy (15, 16).

Patients underwent myomectomy for the following associated symptoms: pelvic pain, menorrhagia, and growth of fibroids, verified by ultrasound. Some women requested myomectomy because of infertility. Exclusion criteria for the investigation were: previous uterine or pelvic surgery, previous abdominal general surgery, presurgical treatment with GnRH analogues (17, 18), gynecologic malignancy, pregnancy, the use of any instillation, such as 32%

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dextran-70, corticosteroids, anticoagulants, and nonsteroidal antiinflammatory drugs, hematologic or coagulation disorders, and the presence of ongoing pelvic infection. In all cases, presurgical evaluation included abdominal and transvaginal ultrasonographic examination and outpatient hysteroscopy to define the size, location, and number of myomas and to exclude additional intracavitary pathologies, i.e., endometrial polyps, hyperplasia, malignancy, or adhesions. All fibroids were identified by standardized transvaginal ultrasound myoma mapping. All patients that had subserous and/or intramural fibroids and transvaginal ultrasound data were recorded for postsurgical evaluation. All women received a standard prophylactic antibiotic dosage of 2 g cefazolin intravenously. All procedures were performed under general anesthesia with endotracheal intubation. This Institutional Review Board–approved project, which allowed the off-label use of Interceed, was conducted from January 2003 to June 2009.

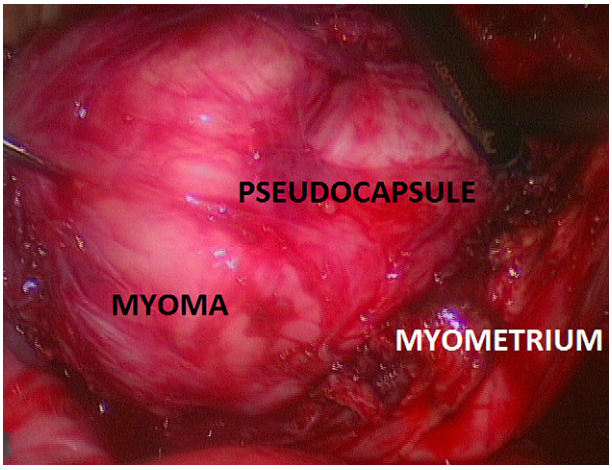
Patients were subdivided into groups for laparoscopic or abdominal surgery based on the technique preferred by surgeons and by surgical skills and expertise. Group 1 included 154 women who underwent abdominal myomectomy plus adhesion barrier (AM + AB). Group 2 included 157 patients who underwent laparoscopic myomectomy plus adhesion barrier (LM + AB). Group 3 included 154 women who underwent abdominal myomectomy without an adhesion barrier (AM no AB), and Group 4 included 155 patients who underwent laparoscopy without an adhesion barrier (LM no AB).

A Pfannenstiel incision was performed for abdominal myomectomy, and laparoscopic procedures followed a standardized four-port approach, one for the laparoscope and three lower quadrant ancillary ports: a 10-mm suprapubic and two 5-mm bilaterally (15, 16). The intracapsular myomectomy was performed by incising the myometrium vertically using a monopolar scalpel after identifying the plane between the pseudocapsule and the myoma. In cases of multiple myomectomy, the surgeon usually incised the myometrium just over each fibroid, but sometimes used one incision to remove more than one myoma. The myomectomy incision was followed by exposure and dissection of the pseudocapsule, by a counter traction of the myoma from the surrounding myometrium (Fig. 1) and excision of the myoma. Myometrial hemostasis was achieved with either bipolar electrosurgical forceps or Vapor Pulse Coagulation (Gyrus Plasma Kinetic AMS, Minneapolis, MN), limiting the thermal spread. In all laparoscopic procedures, myomas were removed using motorized morcellators (Karl Storz Endoscopic Morcellator, Tuttlingen, Germany). The myometrium was sutured using intra- and extracorporeal single or double stitches with 0-absorbable Poliglecaprone monofilament. The clear edges of the uterine defect were approximated with introflexion single U-stitches at 1-cm increments by baseball-type suture. Some cases required two-layer myometrium suturing, and multiple introflexion single stitches were placed at 1-cm increments using extracorporeal or intracorporeal knot tying depending on bleeding. The serosa was repaired with multiple single introflexion stitches. All adhesions were lysed, and normal anatomy was restored in all patients. No hemostatic agents were used. Irrigation solution was aspirated from the pelvis to minimize the risk of the adhesion barrier floating away. In cases of potential postoperative bleeding, a catheter was left in the pelvis for drainage. All patients were instructed to return to the same hospital for further surgery.

After completion of reconstructive uterine surgery, subjects were assigned to the treatment in a 1:1 ratio using a randomization list with random permutated blocks, length of 4. Because the literature lacks data on reoperation rates, the authors hypothesized a rate of reoperation of 30% and a dropout rate of 25%. The randomization list was generated using a Microsoft Excel spreadsheet as described in detail elsewhere (http://www.childrens-mercy.org/stats/plan/random.asp). Block randomization was used to ensure the balance in the number of patients in the four treatment arms. A statistician generated the entire randomization sequence list in advance, and allocations were sequentially numbered from the beginning to end.

FIGURE 1

A laparoscopic myomectomy, with stretching and extracting of the myoma directly from the highlighted surrounding pseudocapsule (on the right).



Tinelli. Adhesion after uterine myomectomy and antibarrier. Fertil Steril 2011.

During the 6-year follow-up interval, a large percentage of women underwent subsequent surgery. Indications for surgery included laparotomy for cesarean section in 35% of cases; other indications were laparotomy or laparoscopy for ovarian cysts, recurrent fibroids, appendectomy, cholecystectomy, extrauterine pregnancy, and infertility. The second surgical team to assess adhesions, was blinded to the initial surgical approach and the use (or not) of the ORC adhesion barrier. Adhesions were described by location and organ involvement of anatomic sites: anterior and lateral parietal peritoneum, uterus, bladder, small bowel, rectosigmoid portion of the large bowel, anterior and posterior cul-de-sac, and right and left adnexal. The quality of adhesions was assessed using the adhesion scoring method of the American Fertility Society (19) according to type: filmy (avascular), organized (vascular and opaque), or cohesive (dense, from serosa to serosa).

The primary and secondary outcomes of the observational analysis were the presence and severity of adhesions, respectively. For sample size calculation, we considered a difference between two populations of $\geq 13\%$ for each procedure to be clinically significant. A power calculation verified that 135 patients in each group would be necessary to detect a difference with an alpha error level of 5% and a beta error level of 80%. Statistical analysis was performed using the statistical program Statview 5.1 for Macintosh (Abacus Concepts, Berkeley, CA). One-way analysis of variance was used to perform the data analysis. The Levene test of homogeneity of variance was used to screen for violations of the assumptions of analysis of variance. Comparisons between two groups with normality and homogeneity of variances were performed by two-tailed unpaired Student *t* test. Alternatively, comparisons between groups with abnormality and heterogeneity of variances were performed by Welch *t* test. Discrete variables were analyzed

with the chi-squared test. A P value of $<.05$ was considered to be statistically significant.

RESULTS

Of the 694 enrolled patients, 546 (78%) were available for assessment of adhesions during a subsequent operation. This included 136/154 of the subjects in group 1 (AM + AB), 138/157 in group 2 (LM + AB), 135/154 in group 3 (AM no AB), and 137/155 in group 4 (LM no AB). There was no statistical difference in comparing participants' baseline characteristics (Table 1) or the interval between the first and the second operations. During the initial surgery, surgical times were shorter for AM (40 and 44 min vs. 91 and 95 min; $P<.01$), but blood loss was less for LM (145 and 150 mL vs. 175 and 180 mL; $P<.01$), with other surgical characteristics similar (Table 2). A catheter was placed in the pelvis for postsurgical drainage in 8.8%–13.8%, and most women had a single fibroid (59.2%–61.5%), with no difference between the groups. The mean diameter of the removed fibroid was between 6 and 8 cm, with no difference between the groups. The percentage of patients with fever >38°C during the first 2 days of hospitalization was minimal in the four groups (from 6.5% to 12.5% of cases), as was the usage of therapeutic postoperative antibiotics (from 5% to 8.8% of cases), with no statistically significant difference.

The incidence and severity of adhesions found during the subsequent surgery was similar for abdominal and laparoscopic myomectomy (Table 3). The highest incidence of adhesions was found in group 3 (28.1%), abdominal myomectomy without adhesion barrier, and the lowest incidence occurred in group 2, laparoscopic myomectomy with barrier (15.9%), and this difference was statistically significant. Adhesions were mostly filmy or organized when an adhesion barrier was used, whereas cohesive adhesions were more common after myomectomy without an adhesion barrier for both laparoscopic and abdominal myomectomy, and the higher incidence of cohesive adhesions in group 3 (AM no AB) compared with groups 1 and 2 (AM + AB and LM + AB) was statistically significant.

DISCUSSION

This study shows that most adhesions were in AM without AB (28.1%), and less were found in LM with AB (15.9%). Most severe adhesions were found after myomectomy without AB for both LM and AM, with higher incidence in AM. In a four-group comparison, the presence of postoperative adhesions were more frequent in AM without AB and least frequent in LM with AB. Thickness was less severe when AB was used regardless of the approach.

Multiple factors can develop new adhesions or worsen existing lesions, including the type of surgery, number of previous surgeries, surgical technique, and the predisposition of individual patients (20). Studies have shown that women who have gynecologic surgery will experience some degree of adhesion formation (21). Once adhesions form, they may recur even after they have been surgically removed. Peritoneal trauma causes a local inflammatory response that leads to fibrin deposition. After peritoneal injury, a local inflammatory response increases capillary permeability, which results in the extravasation of a large volume of serous fluid. The development of fibrinous bands follows in the subsequent hours. During this process, the kinetics of fibrinolysis determines the difference between a physiologic and a pathologic process (22).

It has been suggested that adhesion formation is caused by an imbalance between fibrin-forming (fibrogenesis) and fibrin-dissolving (fibrinolytic) activities in the peritoneum (23, 24). Evidence

TABLE 1

Baseline characteristics of the study participants, mean ± SD.

	Laparotomy plus AB			Laparotomy without AB		
	Group I (n = 136)	Group II (n = 138)	*P* value	Group III (n = 135)	Group IV (n = 137)	*P* value
Age, y	29.8 ± 8.9	30.2 ± 7.5	NS[a]	28.9 ± 9.2	30.1 ± 6.8	NS[a]
BMI, kg/m^2	21.8 ± 1.7	22.9 ± 0.3	NS[b]	22.2 ± 0.9	22.5 ± 0.1	NS[b]
Parity	1.2 ± 0.3	1.3 ± 0.9	NS[b]	1.2 ± 0.7	1.4 ± 0.1	NS[b]
Interval between 1st and 2nd operations, y	2.3 ± 3.8	2.6 ± 0.2	NS[a]	2.4 ± 1.7	2.5 ± 0.8	NS[a]

Note: AB = adhesion barrier.
[a] Unpaired Student *t* test.
[b] Welch *t* test.

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TABLE 2

Initial surgery characteristics of the 546 study participants.

	Laparotomy plus AB			Laparotomy without AB		
	Group I (n = 136)	Group II (n = 138)	*P* value	Group III (n = 135)	Group IV (n = 137)	*P* value
Patients with single fibroid, n (%)	82 (60.2)	85 (61.5)	NS[a]	80 (59.2)	83 (60.5)	NS[a]
Dimension of single fibroid, cm	7 ± 0.7	6 ± 1.5	NS[b]	8 ± 0.4	7 ± 1.3	NS[b]
Women with catheter to drain (removed in 1st day), n (%)	12 (8.8)	16 (11.5)	NS[a]	15 (11.1)	19 (13.8)	NS[a]
Total operative surgical time, min	44 ± 9.3	95 ± 4.7	<.01[b]	40 ± 6.2	91 ± 5.3	<.01[b]
Intrasurgical blood loss, mL	180 ± 3.7	150 ± 4.2	<.01[b]	175 ± 8.1	145 ± 7.7	<.01[b]
Fever, n (%)[c]	12 (12.5)	9 (6.5)	NS[a]	15 (11.1)	11 (8)	NS[a]
Therapeutic postoperative antibiotics administration, no. of patients (%)	9 (6.6)	7 (5)	NS[a]	12 (8.8)	8 (5.8)	NS[a]

Note: AB = adhesion barrier.
[a] χ^2 test.
[b] Welch *t* test.
[c] Patients with fever >38°C after 24 h and for the first 2 days of hospitalization.

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suggests that a posttraumatic insufficiency in peritoneal fibrinolytic activity caused by decreased tPA and increased PAI-1 and PAI-2 permits the deposited fibrin to become organized into permanent adhesions (25). This theory is supported by the observation that women with endometriosis have significantly higher amounts of peritoneal fluid and adhesions, presumably due to an endometriosis-induced low-grade sterile inflammation of the peritoneal cavity (26, 27). A prospective study in humans adds further weight to the hypothesis that adhesions are caused by an insufficiency in peritoneal fibrinolytic activity, and authors also conclude that fibrinolysis is significantly enhanced 1 week after surgery (28).

Two studies showed that adhesions are not reduced when ORC is applied on bleeding or oozing surfaces (29, 30), but other studies have not supported those observations. An investigation compared the efficacy of Interceed with ORC alone. At second-look laparoscopy, there was no significant difference in adhesions in comparing ORC plus heparin (52.5%, 21/40) or ORC alone (65%, 26/40) (31). Another study showed that ORC significantly reduced the incidence and extent of adhesions: Adhesion-free outcomes were 1.5–2.5 times more at sites treated with the AB during laparotomy (32). Studies have shown a further reduction in adhesions with laparoscopy compared with traditional laparotomy (33, 34). The American Society of Reproductive Medicine (ASRM) Practice Committee recommends that efforts to minimize adhesion formation should be used, including minimally invasive techniques and adhesiolysis agents (35).

Experts recommend meticulous procedures, physical separation of denuded or damaged peritoneal surfaces, and placing adhesiolysis agents (36, 37).

Literature reports that the surgical restoration of the uterine anatomy after myomectomy is accompanied by fewer adhesions during second-look surgery (38). Thus, the restoration of the proper anatomic relationships of the pseudocapsule surrounding the myoma (15, 39),

TABLE 3

Adhesion characteristics of the 546 study participants.

	Laparotomy plus AB			Laparotomy without AB		
	Group I (n = 136)	Group II (n = 138)	*P* value[a]	Group III (n = 135)	Group IV (n = 137)	*P* value[a]
Women with adhesions, n (%)	30 (22)	22 (15.9)	NS	38 (28.1)	31 (22.6)	NS
Filmy adhesions (avascular), n (%)	11 (8)	10 (7.2)	NS	10 (7.4)	8 (5.8)	NS
Organized adhesions (vascular and opaque), n (%)	9 (6.6)	7 (5)	NS	12 (8.8)	11 (8)	NS
Cohesive adhesions (serosa to serosa), n (%)	6 (4.4)	5 (3.6)	NS	16 (11.8)	12 (8.7)	NS

Note: AB = adhesion barrier.
[a] χ^2 test with 1 DF.

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should prevent excessive bleeding when removing single or multiple fibroids (15, 16). In fact, the secondary outcomes of our analysis of surgical data showed that blood loss was less for LM, even though the surgical times were shorter for AM. This is probably due to the magnification of endoscope vision, by a superior visualization of the pseudocapsule fibers and blood vessels surrounding the myoma (15, 39), enabling the surgeon to delicately dissect it and to selectively coagulate and cut. Laparoscopic myomectomy is an alternative to laparotomy in many cases. Laparoscopy advantages are short hospitalization, decreased need for postoperative analgesia, and less intraoperative blood loss (40).

Adding tissue separation and protection during the healing process by applying the biocompatible and absorbable ORC AB adherent to traumatized and weeping surfaces (41) further protects against new and recurrent adhesions.

Limitations and biases of this study include the lack of a structured second-look surgery, a loss of follow-up for patients who did not undergo a subsequent surgery, and the noncomparison of this technique between the groups. However, the authors could not propose a standardized second-look laparoscopy in the study protocol for many reasons. Therefore, a longer study interval was needed to recruit and follow subjects to have a satisfactory number of patients who eventually required subsequent surgery.

Because intra-abdominal adhesions are caused by a variety of factors, the combination of laparoscopic intracapsular myomectomy, which limits tissue damage, and the use of an absorbable adhesion barrier is an effective means to minimize adhesion formation. The authors strongly support the ASRM Practice Committee recommendation that that efforts to prevent adhesions should be implemented (35).

CONCLUSION

Adhesion formation after uterine surgery remains a challenge, even with the benefit of adhesion prevention by synthetic barriers (42). Continued efforts are required to improve surgical techniques and antiadhesion agents. In this study, the combined method of laparoscopic intracapsular myomectomy plus ORC absorbable AB reduced the incidence of cohesive postsurgical adhesions.

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