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Review article

Adhesion prevention in laparoscopic myomectomy

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ABSTRACT

Adhesions are common sequels of laparoscopic myomectomy (LM), even though they are much reduced compared with laparotomy. Good surgical technique is the main principle to reduce post LM adhesion. Based on electronic research of the PubMed database using specific keywords, barrier materials offer promise for adhesion prevention at second look laparoscopy. However, pregnancy outcome when influenced by adhesion formation after LM is unclear and warrants further investigation.

Introduction

The frequency of myoma in women of childbearing age is estimated to be 30–80%.[1] The majority of women with myoma are asymptomatic, but some causes are associated with menorrhagia, pelvic pain, or urinary symptoms that cannot be managed by conservative treatment and therefore require surgery. For women who wish to retain their fertility, myomectomy is an alternative to hysterectomy. Myomectomy is one of the pelvic surgeries that could cause a high rate of adhesion. The incidence of adhesion formation after myomectomy was reported to be as high as 83–94%, especially when the myomectomy incision wounds were located at the posterior uterine wall.[2–4] Operation through laparoscopy had less postoperative pelvic adhesion compared with laparotomic surgeries[5] and therefore results in less postoperative morbidity. However, there is controversy. Open surgeries and laparoscopic surgeries were found to be associated with similar rates of adhesion-related readmission in gynecological patients.[6] To date, no definitive strategies, recommendations, or guidelines have been established to prevent the development of pelvic adhesion after myomectomy or laparoscopic myomectomy (LM). The aim of this review is to present clinical studies on various strategies to prevent postoperative adhesion during LM.

Definition of adhesion

Peritoneal adhesions are pathological bands of connective tissue. They may be formed congenitally or acquired, being developed after inflammation or postoperation. The postoperative adhesion formation has been distinguished as: type 1, *de novo* adhesion, which occurs at sites with no adhesion prior to surgery; and type 2, reformation adhesion,[7] which occurs at sites with lysis of adhesion during previous surgery. These adhesion bands may be a thin film of connective tissue, a thick fibrous bridge containing blood vessels and nerve tissue, or a direct contact between two organ surfaces.[8]

To quantify adhesions, the American Fertility Society (AFS) modified the standardized American Society for Reproductive System and developed an adhesion scoring recording system.[9] In this system, 23 individual abdominal and pelvic areas or 13 lower pelvic locations were visualized for severity of adhesion (0, none; 1, filmy, avascular; 2, vascular and/or dense; 3, cohesive) and extent of total area or length of adhesion (0, none; 1, ≤25%; 2, 26–50%; 3, >50%). Second-look laparoscopy (SLL) is a usual way to evaluate postoperative adhesion. Accordingly, the incidence of type 1 adhesion was reported to be 51–95 % at SLL after laparotomic surgeries. This incidence was 12% in laparoscopic surgeries at SLL.[7] Type 2 adhesion occurred in 55–100% of patients regardless of laparotomy or laparoscopy, and is independent of the character of the initial adhesion.[7]

Adhesion formation after LM

LM has become more popular recently, although it is a highly demanding technique. Many strategies have been developed to

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achieve success. Selected cases with two or fewer myomas with 8 cm or less in diameter are suggested for beginners.[10] With more experience, more difficult cases could be attempted with acceptably low complication rates.[11] Modification of surgical technique has been developed to increase feasibility of LM, such as enucleation of myomas,[12,13] and suturing of the myomectomy sites.[14,15] Good surgical technique is related to postoperative adhesion formation.

Post-LM adhesion rate has been reported as 28–88% during SLL.[16–19] This wide range is due to many factors that could influence adhesion formation after LM. Factors that might contribute to a higher rate of adhesion after LM are: higher number of myoma enucleated; greater length of uterine incision; large diameter of the largest myoma; posterior location of the myoma; longer surgical duration; and more surgical knots on myomectomy incision wounds.[18,20–23] Therefore, it is suggested that anti-adhesion devices or techniques are important in LM. However, due to the multiple factors that could influence the development of post-LM adhesion, it is difficult to evaluate the exact efficiencies of these antiadhesion devices or techniques.

Apart from adhesion formation after LM, scars could appear over the myomectomy sites that cause deformity of uterus with unknown significance. Kumakiri et al[24] reported an incidence of 9.2% of this so-called scarred uterus in 692 patients at SLL after LM. Scarred uterus was more likely to occur in patients with preoperative deformed endometrium, complete myometrial penetration of myoma, or multiple enucleated myoma during the operation. Application of adhesion barriers such as Interceed, Seprafilm, or hemostatic preparations such as fibrin glue or sheets has no influence on scar formation.[24]

Adhesion prevention devices

Surgical techniques

Some basic principles during surgery are critical in reducing postoperative adhesions. Meticulous surgical technique in handling tissues, diligence in hemostasis, and avoiding exposure to foreign bodies and drying of tissue are essential. Infection, inflammation, and angiogenesis have a corresponding propensity for adhesion development and should be reduced as much as possible. In laparoscopic surgery, reducing pressure and duration of pneumoperitoneum could decrease adhesion formation.[25] In LM, several studies show that suture technique is closely related to adhesion formation. Pellicano et al[21] has reported that adhesion formation in patients who received subserous sutures was significantly lower compared with patients with a figure-8 stitch over the myomectomy sites. In a multicentre randomized study on 330 laparoscopic surgeries, the antiadhesive 4% icodextrin solution showed no efficacy on adhesion prevention. Instead, length of uterine incision and number of suture knots were significantly associated with *de novo* adhesion formation.[22] In 296 women who received SLL after LM, Kumakiri et al[23] reported that the number of enucleated subserous myoma had an odds ratio of 3.29, and protruding wound an odds ratio of 2.53 on the formation of postoperative adhesion. Good suture technique to resume a smooth serosa surface over the myomectomy incision wound is necessary to reduce postoperative adhesion formation after LM.

Mechanical barriers

Liquid or membrane mechanical barriers may prevent postoperative peritoneal adhesion formation by keeping peritoneal surfaces separate during the critical period of 5–7 days following injury. The results search on PubMed using keywords “LM” and “SLL”, giving the efficiencies of post-LM adhesion prevention on currently commercial antiadhesive products, is shown in Table 1.[16–23,27,29,31,34,38–40]

Prior to the era of well-established adhesion prevention devices, crystalloids such as saline, lactated Ringer’s solution, and dextran solution were used to prevent adhesion. The injured surfaces were separated by the mechanism of hydroflotation or siliconizing effect. However, these solutions are rapidly absorbed and the results of adhesion prevention are either inconsistent or disappointing.[26,27]

Oxidized cellulose

The biodegradable oxidized regenerated cellulose Interceed (Johnson and Johnson Medical, Cincinnati, OH, USA) is the first commercial antiadhesive agent used in LM to prevent postoperative *de-novo* adhesion.[17,27] It was approved for abdominal–pelvic use in European CE Mark and in Asia, but only for laparotomic use by the USA Food and Drug Administration (FDA). It is effective in preventing adhesions but only when there is no blood or excessive peritoneal fluid. However, in a prospective, nonrandomized study including 372 women, Interceed was reported as effective as other adhesion prevention agents under good surgical technique.[28] In a study including 108 patients, the incidence of postoperative adhesion was 38% with the application of Interceed after LM.[23] Other factors such as protruding wound, number of enucleated subserosal myomas, and the diameter of the largest myoma were also associated with postoperative wound adhesion.[23] Interceed is equally effective in different types of myomectomy, laparoscopic, or laparotomy. In an observational study including 694 women receiving either myomectomy or LM with or without Interceed, adhesion rate was higher 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%).[29] Although the differences among these groups were small and with no significance, it was reported that adhesions at SLL were predominant filmy and organized with Interceed, but more cohesive without Interceed.[29]

Natural glycosaminoglycan gel

Cross-linked hyaluronic acid, a natural glycosaminoglycan gel (Hyalobarrier; Fidia Advanced Biopolymers, Abano Terme, Padova, Italy), is a liquid barrier that has a longer residence time in the abdominal cavity. It is approved for abdomino-pelvic use in Europe and Asia. Hyaluronic acid gel was reported effective in preventing post-LM adhesion formation in a randomized control study including 36 infertile women. This study also showed a better adhesion prevention outcome with subserous suture compared with interrupted figure-8 stitch at the myomectomy sites.[21] Pregnancy rates at 1-year follow-up showed parallel results with the antiadhesive outcome.[30] However, in another study including 52 LM patients, the number of patients with an antiadhesive effect of hyaluronic acid was not as significant, but the severity of postoperative adhesion was significantly lower in the hyaluronic acid gel group.[31]

Hyaluronic acid-carboxymethylcellulose film

Hyaluronic acid-carboxymethylcellulose film (Seprafilm; Genzyme Corporation, Cambridge, MA, USA) was approved for abdomino-pelvic use in Europe and Asia, but it was only approved for laparotomy use in the USA. It is completely biodegradable and

Table 1
Summary of studies with or without an application of adhesion barriers in laparoscopic myomectomy followed with a second look laparoscopy.

	Year of publication	Case no.	Adhesion barrier	Period between LM and SLL	Adhesion at SLL	OR (95% CI)
Hasson et al[27]	1992	24	LRS or dextran, promethazine, dexamethasone solution, or Interceed	3.4 wk	66% (21% minimal, 46% moderate or extensive)	
Keckstein et al[16]	1994	22	No treatment	NA	28%	
Mais et al[17]	1995	50	Interceed vs. no treatment	12–14 wk	Interceed: 10/25; 40% No treatment: 22/25; 88%	0.45 (0.18,1.15)
Dubuisso et al[18]	1998	45	No treatment	14.6 ± 13.3 (range, 0.6–49.4) mo	Myomectomy site: 35.6% Adnexal site: 24.4%	
Takeuchi et al[20]	2002	51	Fibrin glue spray	NA	29.4%	
Malzoni et al[19]	2003	18	No treatment	NA	Myomectomy site: 33.3% Adnexal site: 0%	
Pellicano et al[21]	2003	36	Hyalobarrier vs. no treatment	60–90 d	Hyalobarrier: 5/18; 27.8% Figure-8 suture: 44.4% Subcutaneous suture: 11% No treatment: 14/18; 77.8% Figure-8 suture: 89% Subcutaneous suture: 66.7%	0.36 (0.11, 1.20)
Mettler et al[39]	2004	40 (initial including cases: 79.7% LSC)	SprayGel vs. no treatment	3–16 wk	SprayGel: 15/22; 68.2% No treatment: 16/18; 88.9%	0.77 (0.30, 1.96)
Takeuchi et al[38]	2005	91	Fibrin gel vs. Fibrin sheet vs. no treatment	NA	Myomectomy site: Fibrin gel: 10/29; 34.5% Fibrin sheet: 20/30; 66.7% No treatment: 20/32; 62.5% ($p < 0.05$) Adnexal site: Fibrin gel: 2/29; 6.8% Fibrin sheet: 5/30; 16.7% No treatment: 4/30; 12.5%	Myomectomy site: Fibrin gel: 0.55 (0.22, 1.37) Fibrin sheet: 1.07 (0.48, 2.36) Adnexal site: Fibrin gel: 0.55 (0.09, 3.24) Fibrin sheet: 1.33 (0.33, 5.44)
Mais et al[31]	2006	43	Hyalobarrier vs. no treatment	12–14 wk	Hyalobarrier: 8/21; 38.1% No treatment: 13/22; 59.1%	0.64 (0.22, 1.87)
Mettler et al[40]	2008	58 (initial including cases 67.6% LSC)	Hydrogel, (CoSeal, surgical sealant) vs. LRS	8–10 wk	Hydrogel: 13/38; 34.2% Control: 13/20; 65%	0.53 (0.21, 1.35)
Takeuchi et al[28]	2008	372	Fibrin glue ($n = 58$) vs. Fibrin sheath ($n = 73$) vs. Seprafilm ($n = 114$) vs. Interceed ($n = 66$) vs. no treatment ($n = 61$)	NA	Myomectomy site: 37.9% Adnexal site: 8.9%	
Tinelli et al[29]	2011	275	Interceed vs. no treatment	Within 6 y	Interceed: 15.9% (25/138) No treatment: 22.6% (31/137)	0.80 (0.45, 1.43)
Fossum et al[34]	2011	41	Sepraspray ($n = 21$) vs. no treatment ($n = 20$)	4–12 wk	Change of mAFS score over total uterus Sepraspray: 0.68 No treatment: 1.56	
Trew et al[22]	2011	254	Adept ($n = 120$) vs. LRS ($n = 134$)	28–112 d	75.4%, no difference in both groups mAFS score at posterior myomectomy site: Adept ($n = 51$): 5.04 LRS ($n = 48$): 2.71 ($p < 0.007$)	
Kumakiri et al[23]	2012	108	Interceed	6.6 (CI: 5.6–9.2) mo	38%	

CI = confidence interval; LSC = laparoscopic surgery; LRS = lactated Ringer's solution; mAFS = modified American Fertility Society; NA = not applicable; OR = odds ratio; SLL = second look laparoscopy.

effective in the presence of blood. However, it may cause a significant impairment of anastomoses, and should not be applied to anastomosis cases.[32] Seprafilm is brittle and sticky, and requires technical skill and experience for application during laparoscopic surgery.[33] With successful application, Seprafilm is as effective as Interceed and fibrin sealant in preventing postoperative adhesion after LM.[28] Based on the difficulty of Seprafilm application during laparoscopic surgery, a modified hyaluronic acid and carboxymethylcellulose powder with special application device, Sepraspray (Genzyme Corporation, Cambridge, MA, USA) was invented. A pilot study of Sepraspray failed to document its antiadhesive effect[34] and it is no longer used.

Icodextrin

Icodextrin 4% solution (Adept; Baxter Healthcare, Deerfield, IL, USA) is a liquid barrier that could remain in the abdominal cavity for a longer period[35] and has the advantage of easy application during laparoscopic surgery.[36] It was approved by the FDA in 2006 for using in gynecologic laparoscopy, and is the only FDA approved agent for use as an antiadhesive for gynecologic laparoscopy. The antiadhesive effect of Icodextrin was reported as not clinically effective in a randomized study including 264 women.[22] This could be due to multiple factors that influence adhesion formation after LM that are statistically

significantly related to adhesion formation, such as surgery duration, blood loss, number and size of incisions, suturing, and number of knots. However, Adept is still significantly effective at sites with frequent postoperative *de novo* adhesion formation, such as posterior uterus.[22]

Other biological products

Some biological products generally used in other clinical conditions have been applied to LM as adhesion prevention agents. Fibrin glue (Beriplast; CSL Behring, Tokyo, Japan) with two solutions, fibrinogen and thrombin, is commonly used as a hemostatic agent and tissue sealant. It is used with the goal of preventing excess blood loss and as suture support during surgical repair.[37] Fibrin glue was found effective in preventing post-LM adhesion.[38] Another hemostatic agent, Fibrin sheath (Tacho Comb; Tokyo, Japan), however, was ineffective in preventing post-myomectomy site adhesion.[28] Synthetic polyethylene glycol polymer hydrogel solutions, such as SprayGel (Confluent Surgical Inc., Waltham, MA, USA) and CoSeal surgical sealant (Angiotech Pharmaceuticals, Inc., Vancouver, Canada) are used for pericardial adhesion prevention. A Phase III trial and a multicenter randomized study that included patients with myomectomy as well as LM showed that both products are effective but are not significant in reducing adhesion.[39,40]

Overall, these results suggest that good surgical technique alone is insufficient to prevent adhesion formation. Available antiadhesion barriers in current use are mostly effective in reducing post-LM wound adhesion.

Fertility outcome after myomectomy

Adhesion formation after myomectomy could contribute to decrease fertility. Dubisson et al[18] recommend a systematically SLL after LM in patients desiring pregnancy. A lower adhesion rate was found during the third-look procedure (such as laparoscopy or cesarean section) in women who received adhesion lysis in SLL after LM.[4] However, adhesion lysis during SLL found no additional benefit in increasing the subsequent pregnancy rate.[41] Therefore, the exact influence of post-LM adhesion to pregnancy outcome is still unknown.

Apart from postoperative adhesion that might decrease fertility, the location of myoma is another important factor that could affect fertility. Submucosal myomas could decrease fertility outcomes and confer surgical removal. Subserosal myomas are unlikely to affect fertility and do not confer a benefit on removal. Intramural myomas appear to decrease fertility, and the results of removal are still unclear.[42] The type of surgery for myomectomy is another factor that could influence fertility outcome. Laparoscopic myomectomy confer better benefit compared with laparotomic or minilaparotomic myomectomy. In 136 women with symptomatic myoma or unexplained infertility, the cumulative pregnancy rate was higher with LM compared with minilaparotomic myomectomy (52.9% vs. 38.2% after 15 months of follow-up).[43] However, the cumulative pregnancy rate after LM was only 26.7% in women with unexplained infertility versus 73.7% in women without unexplained infertility,[43] suggesting that myoma is not an isolated factor interfering with fertility, and the benefit of myomectomy is difficult to count in women who deserve for pregnancy after surgery. More recently, with an assisted reproductive technique and longer follow-up period after LM, pregnancy rate among infertile women could rise as high as 56–58%.[44] With more meticulous laparoscopic suture technique, less traumatic instruments, and more advanced feasibility such as robot-assisted surgery, pregnancy rates after LM could be even higher, and was reported as 69–74% among infertile women.[11,29,45]

The benefit of using antiadhesive materials after LM in pregnancy outcome is rarely reported. The only literature reported was on autocrosslinked hyaluronic acid gel in infertile women after LM.[21] In nine women who received subserous suture at myoma incision wound followed by hyaluronic acid gel as an adhesion barrier, the pregnancy rate was 100% at 1 year post operation. By comparison, the pregnancy rate in nine women with hyaluronic acid gel and figure-8 stitch at the myoma incision wound were 55.5%. The result was similar to the nine women with subserous suture without hyaluronic acid gel. Pregnancy rate was only 22.2% in the other nine women who received figure-8 stitch on incision wound and no hyaluronic acid gel.[30]

Conclusion

Post-LM adhesion formation is not uncommon and could lead to a poor pregnancy outcome. Apart from a good surgical technique, the application of antiadhesion materials after LM is effective in reducing adhesion formation at SLL. However, more randomized prospective trails are required to establish the best role of different agents together with intraoperative technique to prevent post-LM adhesion formation.

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