REVIEW ARTICLE

Adhesion barriers in laparoscopic myomectomy: Evidence from randomized clinical trials

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Keywords

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Synopsis

Most promising adhesion barriers after laparoscopic myomectomy are oxidized regenerated cellulose, auto-crosslinked hyaluronic acid gel and polyethylene glycol amine plus dextran aldehyde polymers.

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ABSTRACT

Objective: To evaluate the effectiveness of different adhesion barriers in the prevention of *de-novo* adhesion development after laparoscopic myomectomy.

Method: A systematic review was performed by searching seven electronic databases for all randomized clinical trials (RCT) comparing the use of any absorbable adhesion barrier (i.e. intervention group) with either no treatment or placebo (i.e. control group) in the prevention of adhesion development after laparoscopic myomectomy.

Results: Eight RCT with a total of 748 participants (392 in the intervention group and 356 in the control group) were included. The assessed adhesion barrier methods were: the oxidized regenerated cellulose (ORC) in 2 studies, the auto-crosslinked hyaluronic acid (HA) gel in 2 studies, the 4% icodextrin solution in one study, the modified HA and carboxy-methylcellulose in one study, the polyethylene glycol ester trilysine amine solution plus a borate buffer solution in one study, and the polyethylene glycol amine plus dextran aldehyde polymers in another study.

Conclusions: Adhesion barriers methods showing the most promising results were: ORC, auto-crosslinked HA gel and polyethylene glycol amine plus dextran aldehyde polymers.

1 INTRODUCTION

Postoperative adhesions that form in the abdomen after pelvic or abdominal surgery are the physiological reaction to the peritoneal surfaces damage and they represent the most common complication of abdominopelvic procedures [1–3]. Adhesions may vary from a thin layer of connective tissue to strict links between surfaces or pathological bonds with nerves and blood vessels, either in abdomen or in pelvis [4-6]. In pelvis, in particular, gynecological surgical procedures can lead to fibrotic connections involving rectosigmoid genital organs, bowel loops, urinary bladder, ureters and pelvic wall [7]. Laparoscopic myomectomy is the elective surgical technique to treat intramural or sub-serosal leiomyomas in symptomatic women with abnormal uterine bleeding or bulk-related symptoms and wishing to maintain their fertility [8]. Despite continuous improvements in surgical procedures, especially in minimally invasive techniques, the adhesion development rate remains high, up to 50% after laparoscopic myomectomy and up to 94% of patients undergoing laparotomic myomectomy [9,10]. Adhesions represent a serious health care concern due to their consequences, such as chronic pelvic pain, risk of bowel obstruction, complicated subsequent surgical procedures and female infertility [11–13]. In fact, pelvic adhesions were proven to be present in 15% to 40% of infertile women [14].

Postoperative adhesions formation seems to be multifactorial. Length and location of the uterine incisions and the size and number of myomas, besides duration of the surgical procedure, blood loss, and history of previous surgeries have been proposed as factors contributing to adhesion development after myomectomy [6,15,16].

Great attention is focused on adhesion prevention strategies. Besides minimizing surgical trauma, the application of several different anti-adhesion barriers has been suggested [17,18]. Anti-adhesion materials include natural and synthetic agents. Natural materials are widely used; they include in particular hyaluronic acid (HA), cellulose and its derivates, dextran, and icodextrin. Among synthetic polymer materials, polyethylene glycol (PEG), polyglycolide, polyecaprolactone and polyvinyl alcohol have been employed [19]. Although a recent comprehensive Cochrane Review showed limited efficacy of some adhesion barriers in decreasing de-novo adhesion development after gynecological surgery, it did not specifically investigate the role of anti-adhesion agents after laparoscopic myomectomy except for the fibrin sheet application [20].

This systematic review of randomized clinical trials aimed to evaluate the effectiveness of different adhesion barriers in the prevention of adhesion formation after laparoscopic myomectomy.

2 MATERIALS AND METHODS

Study protocol

All review steps were performed following a study protocol for systematic reviews designed *a priori***.** The study was reported following the Preferred Reporting Item for Systematic Reviews and Meta-analyses (PRISMA) statement [21].
Review Manager 5.3 software (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014) was used.

Search strategy

MEDLINE, Scielo, EMBASE, ClinicalTrials.gov, Scopus, Sciencedirect, and the Cochrane Library at the CENTRAL Register of Controlled Trials were searched as electronic databases from their inception until March 2020. Several searches were performed by using combinations of the following terms: “randomised”, “randomized”, “laparoscop*”, “myomectomy”, “myoma”, “adhesion”, “robotic”, “prevention”, “barrier”, “spry”, “review”, “clinical trial”, “oxidized regenerated cellulose”, “hyaluronic acid”, “carboxy-methylcellulose”, “dextran”, “icodextrin”, “polyethylene glycol”, “polyglycolide”, “polyecaprolactone” and “polyvinyl alcohol”. Moreover, references of the eligible articles were assessed in order to find studies missed by the electronic databases search. No exclusion criteria for geographic location or language were imposed.

Selection criteria

All randomized clinical trials comparing the application of any absorbable adhesion barrier (i.e. intervention group) with either no treatment or placebo (i.e. control group) in the prevention of *de-novo* adhesion formation after laparoscopic myomectomy were included. We excluded trials recruiting women undergoing open myomectomy or hysterectomy, and quasi-randomized trials.

The electronic search and the eligibility assessment of the trials were independently performed by two authors (GB, DR). Disagreements were discussed collectively with a third author (AR).

Data extraction

Data were extracted without modifications from the included studies according to the PICO [16].

"Population" was women undergone laparoscopic myomectomy.

"Intervention" was the adhesion barrier adopted.

"Comparator" was either placebo or no treatment in the prevention of *de-novo* adhesion formation.

"Outcome" was the incidence of adhesions at second-look surgery, defined as follows:

- number of patients with de novo adhesions at second-look surgery;
- *total adhesions score*, defined as the sum of the scores at different abdomino-pelvic anatomical sites assigned according to "The Operative Laparoscopy Study Group scoring system" or the "American Fertility Society" modified score (mAFS).

In "The Operative Laparoscopy Study Group scoring system" adhesions are scored as follows: 0, no adhesion; 1, filmy and avascular; 2, dense and/or vascular and 3, cohesive. The mAFS evaluates incidence (presence or absence), severity ('filmy' or 'dense and vascular') and extent (',1/3', '1/3–2/3' or '.2/3') of adhesions [22,23].

- *uterine adhesions score*, defined as the adhesion score at uterine walls (according to "The Operative Laparoscopy Study Group scoring system" or the mAFS) and eventually subdivided into posterior and anterior based on the uterine localization of the myomas;
- *uterine adhesions score corrected for baseline adhesions status*, defined as difference between uterine adhesion score at baseline and at second-look surgery.

Two authors (GS, MM) independently performed data extraction.

Risk of bias within studies assessment

The risk of bias within studies was evaluated according to the criteria suggested in the *Cochrane Handbook for Systematic Reviews of Interventions*. For each included study seven domains related to risk of bias in treatments effect estimates were investigated: 1)

random sequence generation; 2) allocation concealment; 3) blinding of participants and personnel; 4) blinding of outcome assessment; 5) incomplete outcome data; 6) selective reporting; and 7) other bias. Authors evaluated each trial as “low risk”, “high risk” or “unclear risk” of bias [24].

Two authors (GB, EDE) independently performed the risk of bias within studies assessment. Disagreements were discussed collectively with all Authors until a consensus was reached.

3 RESULTS

Study selection and study characteristics

The whole process of study selection is shown in in Figure 1.

Eight RCT with a total of 748 participants (392 in the intervention group and 356 in the control group) were included [6,25–31]. The assessed adhesion barriers were the oxidized regenerated cellulose (ORC) in two studies [25,27], the auto-crosslinked HA gel in two studies [28,31], the 4% icodextrin solution in one study [30], the modified HA and carboxy-methylcellulose (CMC) in one study [26], the polyethylene glycol ester trilysine amine solution plus a borate buffer solution in one study [29] and the polyethylene glycol amine plus dextran aldehyde polymers in another study [6]. All studies compared adhesion barrier application with no treatment, with the exception of one study that compared adhesion barrier with placebo (i.e. Ringer’s solution) [30]. Definition of adhesions at the second-look surgery followed the scoring system of the Operative Laparoscopy Study Group in two studies [27,28] and of the American Fertility Society (AFS) (or a its modified version) in the other six studies. Regarding industrial funding supporting the primary studies, four out of the eight included studies reported an industrial sponsorship [6,26,29,30].

Characteristics of each included study is shown in detail in Table 1.

Patients’ characteristics

Mean age of patients ranged between 28.8 and 37 years in the intervention group, and 30.1 and 44.3 years in the control group. Body mass index (BMI) ranged between 22.9 and 29 kg/m^2 in the intervention group, and 22.5 and 27 kg/m^2 in the control group. Prior abdominal surgery was not stated in 4 studies [27,28,30,31], absent for both groups in one study [25], and present in the 43.9% (62.0% in the intervention versus 25.0% in the

control cohort) and 46.7% (44.4% in the intervention group versus 50.0% in the control group) respectively in other two studies [26,29]. Prior myomectomy was not reported in 4 studies [27–29, 31], absent in one trial [25], and present in 19.5% of patient in one study (24.0% in the intervention versus 15.0% in the control arm) [26], while it was considered as an exclusion criterion in another study [30]. Trew et al. reported the previous surgery rate for all the randomized patients (not only the women included in the laparoscopic myomectomy sub-study): 33.3% referred prior gynecological surgery, of whom 14.1% underwent previous myomectomy [6].

The mean number of myomas laparoscopically removed ranged between 1.8 and 3.2 in the intervention group, and 1.7 and 3.6 in the treatment group, while the size of the largest removed myoma ranged between 4.3 and 6.9 cm in the intervention group, and 4.5 and 7.0 cm in the control group. Incision technique and/or energy source were reported in five out of the eight included studies [26, 28–31].

The operative time ranged between 45 to 130 min. Concomitant surgery to laparoscopic myomectomy was not stated in five studies [26,27,29–31] while was absent in one study [25], present in nine women in the intervention group and in 11 women in the control group in one study [28], present in 12 women in the intervention group and in nine in the control group in another trial [6].

Follow-up period ranged from 2 to 78 months with a time to second-look surgery ranged from 21 to 949 days.

Details about patients' characteristics and laparoscopic myomectomy are reported in Tables 2 and 3, respectively.

Risk of bias within studies

The seven domains described in the Cochrane Handbook for Systematic Reviews of Interventions were adopted for the quality assessment of the studies included in this systematic review. Most of the included trials were categorized at "low risk" of bias in most of the seven Cochrane domains related to the risk of bias. In particular, all the included studies were at low risk of bias in the "random sequence generation", "allocation concealment", "incomplete outcome data" and "selective reporting" domains.

In contrast, all the studies except for one [30] were judged at unclear [6,29] or high risk [25–28,31] of performance bias; indeed, patients and/or surgeons were not blinded about the adhesion barrier administration after laparoscopic myomectomy.
Regarding the risk of detection bias four trials were considered at high risk of bias, since the outcome assessment could have been influenced by a lack of complete blindness [25–27,31].
Lastly, in the "other bias" domain, two studies [27,31] were judged at unclear risk of bias, and three studies [6,25,26] at high risk of bias. In particular, data about previous or concomitant surgery [6,27,31], other pelvic pathologies [6,25,27,31], and myomectomy technique [6,25,27] were missing. Moreover, in the study by Tinelli et al. [25], the follow-up length was remarkably longer than in the other included studies, while in the trials by Trew et al. and Tinelli et al. the second-look surgery for adhesions assessment was performed based on clinical indication [6,25]. Finally, in Fossum et al. RCT [26], three control patients failed to complete the second-look surgery (Figure 2).

Synthesis of results

ORC

Two studies assessed the efficacy of ORC in the prevention of adhesions after laparoscopic myomectomy [25,27]. The incidence of adhesions at second-look-surgery was significantly lower in the intervention group compared to the control group in one study ($p<0.05$) [27], while such a difference was not significant in the other one [25]. However, when considered the total adhesion score at the second-look surgery, the difference was significant in both trials ($p=0.0026$ and $p=0.0021$, respectively) (Table 4).

Auto-crosslinked HA gel

Two studies assessed the efficacy of auto-crosslinked HA gel [28,31]. Although Pellicano et al. found a significant decrease in the incidence of adhesions in the intervention group [26], such decrease was not significant in the other study (relative risk=0.64; $p=0.17$). Mais et al. found no significant differences even in total and uterine adhesion scores; the only significant decrease was found when the uterine score was corrected for the baseline adhesions status of the patients ($p=0.03$) [28] (Table 4).

4% Icodextrin solution

4% icodextrin solution was evaluated in one trial [30]. Such an adhesion barrier showed a significant decrease in the uterine adhesion score in the intervention group only for a posterior localization of myomas (p=0.007); differences between groups were not significant when considering the incidence of *de novo* adhesions (odds ratio=1.11; p=0.693), the total adhesion score and the uterine score for an anterior localization of myomas (Table 4).

Modified HA and CMC

Modified HA combined with CMC was assessed in one trial [26], that showed no significant differences in the incidence of adhesions and in the uterine score corrected for baseline adhesions status of the patients between the intervention and the control groups (Table 4).

Polyethylene glycol ester trilysine amine solution plus a borate buffer solution

Polyethylene glycol ester trilysine amine solution plus a borate buffer solution as adhesion barrier was evaluated in one study [29]. No significant differences were found in the incidence of adhesions and in the uterine score assessing the severity, the extent and the area of sites adherent to the uterus between the intervention and the control group (Table 4).

Polyethylene glycol amine plus dextran aldehyde polymers

One study investigated the anti-adhesive efficacy of polyethylene glycol amine plus dextran aldehyde polymers and reported a statistically significant decrease in the total score at second-look surgery after laparoscopic myomectomy between the treatment and the control group [6]. Furthermore, when considering all the operated sites throughout the abdominal cavity, the adjusted difference between groups represented a statistically significant 49.5% reduction in adhesion score for intervention patients compared with controls ($p < 0.01$) (Table 4).

5 DISCUSSION

Main findings

This systematic review aimed to evaluate the effectiveness of different adhesion barriers in the prevention of adhesion formation after laparoscopic myomectomy.

Among natural materials, ORC was found to be effective in reducing the total adhesion score at the second-look surgery in both the included trials and the incidence of de novo adhesions in one study [25,27]. One trial found a significant decrease in the incidence of de novo adhesions in the auto-crosslinked HA gel group compared to placebo [31]; the second trial showed a significant decrease in the uterine adhesion score corrected for the baseline adhesions status [28]. Modified HA combined with CMC did not reduce adhesions incidence [26], as well as 4% icodextrin solution [30]. This latter showed a significant decrease in the uterine adhesion score in the intervention group only for posterior localization of myomas [25].

Regarding synthetic materials, polyethylene glycol ester trilysine amine solution plus a borate buffer solution did not demonstrate any significant difference in adhesions incidence and in uterine score assessing adhesions' severity, extent and area between the intervention and the control group [29]. Polyethylene glycol amine plus dextran aldehyde polymers showed a significant reduction of total adhesion score between treatment and control group [6].

Interpretation

Although evidences are available regarding the efficacy of several adhesion barriers in limiting de-novo adhesion development, a recent comprehensive Cochrane Review did not find any significant effect of these agents on pelvic pain and fertility outcomes after gynecological procedures [5,20]. However, this Cochrane Review did not specifically investigate the role of adhesion barriers after laparoscopic myomectomy except for the fibrin sheet application [20]. Among available adhesion barriers, natural materials or their combinations seem to have been the most widely used [19]. The first anti-adhesion product approved by US Food and Drug Administration was an ORC membrane, which showed a significant anti-adhesion effect in animal models, besides an extreme biocompatibility [33]. In vivo, ORC was proven to allow a reduction in adhesions re-formation in general and gynecological surgery at both laparotomy and laparoscopy [34]. Nevertheless, the ORC membrane should not be applicated to bleeding surfaces; indeed, the presence of blood risks to bother its effectiveness in preventing fibrotic bonds development [35]. CMC showed high biocompatibility and thermal stability in animal

models and in vivo [19]. Both ORC and CMC-based barriers appeared to be effective in limiting de-novo adhesion development after minimally-invasive myomectomy in a recent literature review and meta-analysis [7]. Our results confirm the ORC role in reducing adhesion extent and severity at second-look surgery [25,27].

HA has shown several anti-adhesive properties: it inhibits the inflammatory cascade blocking granulocytes activity (with a concentration and molecular weight-related positive correlation) and it stimulates fibrin dissolution and proliferation of mesothelial cells promoting wound healing. Nevertheless, the application of HA in vivo upon scarified areas is often irregular, and the molecule is quickly degraded and re-absorbed [36]. In order to increase HA duration at surgical site, pre-clinical researches focused on its cross-linking, that provided a longer residence time in animal models [37,38]. Clinical studies confirmed the relevant anti-adhesion role of cross-linked HA [39]. Thus, auto-crosslinked hyaluronan gel has been introduced, allowing to avoid potential risks related to the introduction of foreign bridge molecules [28]. Our results about auto-crosslinked HA application after laparoscopic myomectomy are controversial; only one trial showed a significant reduction of de-novo adhesion in the study group compared to the placebo cohort [31]. The first sodium hyaluronate–carboxymethylcellulose (HA–CMC) was developed with the aim to combine CMC and HA properties. This way, HA half-life and its effect on the scarified surface are prolonged, providing a long-lasting anti-adhesive barrier [26]. Moreover, HA–CMC can be safely applied even in presence of blood [40]. Fossum et al. reported that the application of a modified HA and CMC powder after laparoscopic myomectomy did not demonstrate any difference in the incidence of adhesions between the intervention and the control groups. A non-significant increase in adhesion scores at anterior, posterior and entire uterus was noted in the control cohort [26].

4% icodextrin solution is a non-viscous, iso-osmotic, high-molecular-weight polymer solution, that once injected into the abdominal cavity temporarily keeps peritoneal surfaces separated, providing a barrier to adhesion formation [41]. Due to its fluid nature icodextrin solution was proposed for intraoperative and postoperative irrigation after several abdomino-pelvic surgical procedures, showing some evidences of effectiveness [42]. We found one RCT comparing the use of 4% icodextrin solution to lactated Ringer's solution after laparoscopic myomectomy, that did not show any difference in de-novo

adhesions incidence between intervention and control groups. A slight decrease in uterine adhesion score was evidenced in the intervention group, only for posterior localization of myomas [30].

Regarding artificial adhesion barriers, PEG use has been widely described [43]. According to Li et al., this polymer seems to act with differ pathways. Due to its high viscosity, it avoids the contact of intraperitoneal nearby structures. In addition, it exerts osmotic pressure increasing the formation of peritoneal fluid and decreasing inflammation. Moreover, animal models showed that it aggregates with intra-peritoneal proteins, retarding its re-absorption [19]. PEG has been associated with a variety of synthetic/natural molecules in order to improve its anti-adhesive and time-related properties. Regarding laparoscopic myomectomy, our research found out two RCTs investigating PEG application compared to placebo. In one trial polyethylene glycol ester trilysine amine solution associated with a borate buffer solution showed no significant differences in the adhesion incidence and in the uterine adhesion scores between the intervention and the control group [29]. Trew et al. investigated the application of a mix of two aqueous solutions, polyethylene glycol amine polymers and dextran aldehyde. When sprayed together, the components form a hydrogel that covers scarified surfaces. The hydrogel group showed a significant reduction in the total adhesion score at second-look surgery compared to the control group (no intervention) [6].

Altogether, only two of the eight included trial found a statistically significant decrease in de-novo adhesion development in the intervention at second-look surgery after laparoscopic myomectomy. Both the trials investigated the employ of natural polymers as adhesion barriers (ORC and auto-crosslinked HA gel, respectively) after 60 to 98 days from their application [27,31]. Three authors demonstrated a reduction in total score at second-look surgery in the intervention group compared to the control cohort with the use of ORC and a mix of polyethylene glycol amine polymers and dextran aldehyde [6,25,27]. Only one trial reported some evidences of uterine score reduction at posterior uterus after the application of adhesion barriers [30]. A remarkable heterogeneity between the included studies was found and could have affected the results reporting.

It would be interesting to investigate adhesion barriers possible efficacy on long term outcomes, such as infertility, small bowel obstruction, and chronic abdomino-pelvic pain, that was not evidenced.

Lastly, about safety of the anti-adhesion agent, four out of the randomized clinical trials evaluated it as a primary or secondary outcome. They confirmed the good safety profile of auto-crosslinked HA gel, 4% icodextrin solution gel, modified hyaluronic acid and CMC and dextran aldehyde plus polyethylene glycol amine polymers [6,26,28,30]. None of the selected studies reported any serious adverse event nor complication related to anti-adhesion materials application.

Strength and limitations

Strengths of this systematic review include the methodological approach, which complied with the Cochrane Handbook for Systematic Reviews of Interventions guidelines. Moreover, the included studies showed low risk of selection bias and attrition bias and reporting bias.

Limitations of this study may be the different inclusion and exclusion criteria adopted by the authors for participants' selection. In addition, Mais et al.'s trial was conducted in 1995, eventually implying a change in the operative technique [27]. Heterogeneity between the included studies concerning myomectomy techniques, previous or concomitant abdominal-pelvic surgery, presence of endometriosis or other pelvic disease, follow-up duration and time to second-look surgery have influenced adhesions evaluation at baseline.

Conclusion

Adhesion barriers methods that seemed to show the most promising results in reducing the incidence of adhesions after laparoscopic myomectomy were ORC and the auto-crosslinked HA gel among natural materials, and polyethylene glycol amine plus dextran aldehyde polymers among synthetic materials. Modified HA combined with CMC and 4% icodextrin solution did not show a decrease in adhesions incidence in the natural materials group, as well as polyethylene glycol ester trilysine amine solution plus a borate buffer solution in the synthetic materials group. No complications or serious adverse event related to barrier agent application were reported. Despite a non-negligible risk of bias in some domains, this may be the highest evidence in the field. Further RCTs are necessary to confirm and integrate these findings.

Author Contributions

GB: study conception, study design, study methods, data extraction, data analysis, manuscript preparation

AR: study conception, study design, study methods, data analysis, manuscript preparation, methods supervision

DR: study conception, study design, study methods, data extraction, data analysis, manuscript preparation

GS: study design, study methods, data analysis, manuscript preparation

AT: study conception, study design, study methods, data analysis, manuscript preparation

EDE: study conception, data extraction, data analysis, manuscript preparation

MM: data extraction, data analysis, manuscript preparation

PS: study design, data analysis, manuscript preparation, methods supervision

FZ: study design, methods supervision, whole study supervision

RS: study conception, study design, methods supervision, whole study supervision

Conflicts of Interests

The authors have no conflicts of interest.

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FIGURE LEGENDS

Figure 1. Flow diagram of studies identified in the systematic review. *(PRISMA template [Preferred Reporting Item for Systematic Reviews and Meta-analyses]).*

Figure 2. Assessment of risk of bias. (A) Summary of risk of bias for each trial; Plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all the included studies.

Study	Study location	Study design	N of centers	Months of	Lost to f-	N of patients	Inclusion criteria	Exclusion criteria	Intervention group	Control group	Primary outcome	Definition of

Table 1. Characteristics of the included studies.

				study	up	[treatment vs control group]						adhesions
1995 Mais	University hospital, Italy	RCT	1	18	0	50 (25 vs 25)	- Absence of adhesions - absence of associated lesions - subserous/intramural myomas - 1 to 4 myomas - Size of largest myoma: 3 to 6 cm	-	LPS myomectomy + ORC	LPS myomectomy	Efficacy of ORC barrier in prevention of de-novo adhesion formation	Operative Laparoscopy Study Group, 1991
2003 Pellicano	University hospital, Italy	Prospective RCT	1	10	0	36 (18 vs 18)	-Infertile women with symptomatic uterine fibroids	-	LPS myomectomy + auto-crosslinked HA gel	LPS myomectomy	Efficacy of auto-crosslinked HA gel in adhesion prevention after LPS myomectomy	AFS
2006 Mais	University hospitals, Italy	Observer-blind, multicenter RCT	4	24	9 (5 vs 4)	43 (21 vs 22)	-Premenopausal -non-pregnant -Largest myoma 2 to 5 cm	- diabetes, hepatic disorders, renal disorders, severe cardiopathies, malignancies	LPS myomectomy + auto-crosslinked HA gel	LPS myomectomy	Applicability, safety and efficacy of an auto-crosslinked	Operative Laparoscopy Study Group, 1991

								-Previous of anti-adhesive measures -Abdominal / pelvic infection - Oral steroids / Immunosuppressive / cytostatic treatments - pregnancy - coagulation disorders - insufficient intraoperative haemostasis			HA gel in preventing adhesion formation after LPS myomectomy	
2011 Trew	European University Hospitals	Multicentric Double-blind RCT	25	20 weeks	-	254 (134 vs 120)	-18-45 years old - Not pregnant	- pregnancy (including ectopic) - Serum GOT/GPT and/or bilirubin > 20% normal - Blood urea nitrogen and creatinine >30% normal - systemic corticosteroids, antineoplastic drugs	LPS myomectomy + 4% Icodextrin solution (Adept ®) [intraoperative irrigating solution and 1 L postoperative instillate]	LPS myomectomy + Ringer's solution [intraoperative irrigating solution and 1 L postoperative instillate]	Safety and efficacy of 4% Icodextrin solution in reduction of de novo adhesion formation	mAFS

								and/or radiation - GnRH agonist/antagonists in 4 weeks prior - pelvic or abdominal infection - allergy to starch-based polymers - intolerance / hypersensitivity to study materials - Prior surgery for myomas - Non-gynecological surgical procedures planned before LPS - > than 4 myomas on US - largest myoma < 2 cm or > 8 cm on preoperative US - substance and/or alcohol abuse - Use of another investigational agent				

								- Participation in a clinical trial within the last 30 days - Diabetes mellitus (France only)				
2011 Tinelli	University Hospitals	Multicentric Prospective blinded randomized study	-	78	0	275 (138 vs 137)	- pelvic pain - menorrhagia - growth of fibroids verified by US - infertility	- Previous pelvic surgery - Previous abdominal general surgery - Presurgical GnRH analogues - Gynecologic malignancy - Pregnancy - Current use of instillation - current use of corticosteroids, anticoagulants, NSAID - Hematologic / coagulation disorders - ongoing PID	LPS myomectomy + ORC	LPS myomectomy	Efficacy of ORC barrier in prevention of de-novo adhesion formation	AFS

2011 Fossum	Reproductive endocrinology and infertility clinics	Multicenter, reviewer-blinded RCT	3	-	3 (0 vs 3)	41 (21 vs 20)	-Non-pregnant women - 18 – 49 years old - scheduled for LPS myomectomy	- PID / abdominal abscess - Surgical entry in endometrial cavity or bowel lumen - adhesiolysis involving the bowel - concurrent, non-gynecologic procedure	LPS myomectomy + modified HA and CMC adhesion barrier	LPS myomectomy	Safety and efficacy of a modified hyaluronic acid and CMC adhesion barrier after LPS myomectomy	AFS
2014 Tchartchian	University Hospital, Germany	Prospective, blinded RCT	1	8-12 weeks	2	15 (9 vs 6) randomized 13 (8 vs 5) analyzed	- ≥ 18 years old - child-bearing potential - at least 1 myoma	-Pregnancy or lactation - Prior open or closed myomectomy - active endometriosis or infection - active IBD or PID - frozen pelvis - hydrosalpinges	LPS myomectomy + SprayShield ™ Adhesion Barrier (polyethylene glycol ester trilysine amine solution plus a borate buffer solution)	LPS myomectomy	Incidence, severity and extent of uterine adhesions	mAFS

2017 Trew	European tertiary referral centers for gynecologic laparoscopy	Prospective, multicenter, controlled, blinded RCT	4	7 months	1 (1 vs 0)	34 (18 vs 16)	- premenopausal - 18-46 years old - wish to maintain fertility - LPS myomectomy (pure or hybrid)	-	LPS myomectomy (pure or hybrid) + dextran aldehyde and polyethylene glycolamine polymers (Actamax Surgical Materials LLC, Wilmington, DE))	LPS myomectomy (pure or hybrid)	primary outcomes: safety secondary outcome: efficacy (incidence, severity, extend and adhesion score at 16 sites)	Combined score of the severity and extent of adhesions at each of 16 anatomical sites and 5 regions.

RCT: randomized clinical trial
LPS: laparoscopy
PID: pelvic inflammatory disease
ORC: oxidized regenerated cellulose
HA: hyaluronic acid
CMC: carboxy-methylcellulose
mAFS: modified American Fertility Society
-: not stated or not assessed

Author	Age (years old) (mean + SD) [treatment vs control group]	BMI (kg/m^2) [treatment vs control group]	N of myomas [treatment vs control group]	Size of the largest myoma (cm) [treatment vs control group]	Site of myomas (N) [treatment vs control group]
1995 Mais	34.1 ± 5.7 vs 33.2 ± 5.5	-	2.2 ± 0.8 vs 2.0 ± 0.9	4.3 ± 0.9 vs 4.5 ± 0.9	Subserous or intramural
2003 Pellicano	28.8 ± 4.1 vs 30.7 ± 2.6	-	2.1± 0.4 vs 1.9 ± 0.5	6.9 ± 1.2 vs 6.1 ± 1.5	Anterior face 1.2 ± 0.3 vs 1.3 ± 0.4 Posterior face 1.4 ± 0.3 vs 1.3 ± 0.2
2006 Mais	33 ± 5 vs 34 ± 5	-	1.8 ± 0.9 vs 1.7 ± 0.9	4.3 ± 1.2 vs 4.5 ± 1.1	Subserous 1.0 ± 1.1 vs 1.0 ± 0.8 Intramural 0.8 ± 0.8 vs 0.7 ± 0.7
2011 Trew	35.5 ± 5.1 vs 35.3 ± 4.9	-	-	-	Posterior 52 vs 54 women Anterior 39 vs 34 women Anterior + Posterior 43 vs 32 women
2011 Tinelli	30.2 ± 7.5 vs 30.1 ± 6.8	22.9 ± 0.3 vs 22.5 ± 0.1	-	6.0 ± 1.5 vs 7.0 ± 1.3	Subserous or intramural
2011 Fossum	37 vs 36	29 vs 27	3.2 ± 2.7 vs 3.6 ± 3.2	-	-
2014	35.8 ± 4.6 vs 44.3 ± 3.3	-	1 myoma 6 (66.7%) vs 3	4.6 ± 1.5 vs 4.5 ±	Intramural-subserosal –

Tchartchian			(50.0%) 2 myomas 1 (11.1%) vs 1 (16.7%) 3 myomas 2 (22.2%) vs 2 (33.3%)	1.2	submucosal
2017 Trew	33.6 ± 5.9 [32.7 ± 5.7 vs 34.1 ± 5.5] *	24.8 ± 5.5 [25.4 ± 6.7 vs 24.5 ± 4.2] *	3.0 ± 2.1 [2.9 ± 2.0 vs 3.1 ± 2.3] *	-	-

TABLE 2 Women characteristics

BMI: body mass index

-: not stated or not assessed

**data referring to all the study population (not only to the myomectomy subgroup)*

Study	Patients with adhesions [treatment vs control group]	Patients without adhesions [treatment vs control group]	Operative time (min) [treatment vs control group]	Total score at baseline [treatment vs control group]	Uterine score at baseline [treatment vs control group]	Concomitant surgery (N) [treatment vs control group]	Incision technique (N) (treatment vs control group)	Number of hysterotomic incision N ± SD ([treatment vs control group]
1995 Mais	0	50	45 to 130	-	-	-	-	Anterior face 10 vs 11 Fundal 17 vs 13 Posterior 9 vs 10
2003 Pellicano	-	-	-	-	-	-	Unipolar incision 18 vs 18	Anterior face 1.2 ± 0.3 vs 1.3 ± 0.4 Posterior face 1.4 ± 0.3 vs 1.3 ± 0.2
2006 Mais	Not stated	Not stated	Not stated	1.4 ± 2.4 vs 1.7 ± 2.5	0.2 ± 0.7 vs 0.1 ± 0.5	20 (9 vs 11)	Clod blade 4 vs 4 ultrasonic 8 vs 12 Monopolar 4 vs 2 Bipolar 0 vs 2 Not recorded 5 vs 2	Total 1.6 ± 0.9 vs 1.8 ± 0.9 Anterior 0.6 ± 0.7 vs 0.5 ± 0.6 Fundic 0.5 ± 0.6 vs 0.7 ± 0.6 Posterior 0.5 ± 0.6 vs 0.5 ± 0.8

2011 Trew	-	-	103.4 ± 46.4 vs 99.9 ± 43.4	-	-	-	Grasping forceps or myoma screw	1.75 ± 1.11 vs 1.48 ± 0.73
2011 Tinelli	-	-	95 ± 4.7 vs 91 ± 5.3	-	-	0	-	-
2011 Fossum	25 (61.0%) [15 (71.4%) vs 10 (50%)]	16 (39%) [6 (28.6%) vs 10 (50%)]	Median 102 vs 99	-	-	-	Electrosurgery 1 vs 3 Harmonic scalpel 13 vs 12 Laser 8 vs 7	-
2014 Tchartchian	9 (60%) [6 (66 .7%) vs 3 (50%)]	6 (40%) [3 (33.3%) vs 3 (50%)]	-	-	N of sites adherent to the uterus 0.5 ± 1.1 vs 0.0 ± 0.0 - severity score of sites adherent to the uterus 0.29 ± 0.55 vs 0.0 ± 0.0 - Mean extent of sites adherent to the Uterus 0.42 ± 0.85 vs 0.0 ± 0.0 - Area of sites adherent to the	-	Grasping forceps or myoma screw	1 incision 7 (77.8%) vs 3 (50.0%) 2 incisions 1 (11.1%) vs 1 (16.7%) 3 incisions 1 (11.1%) vs 2 (33.3%)

					uterus 4.13 ± 9.03 vs 0.0 ± 0.0 (cm^2)			
2017 Trew	47/63 [(74.6%) 29/33 (87.9%) vs 18/30 (60.0%)] *	16/63 (25.4%) [4/33 (12.1%) 12/30 (40.0%)] *	90.8 ± 48.7 [91.7 ± 44.9 vs 89.8 ± 57.3] *	1.52 ± 1.22 vs 0.90 ± 1.30	-	21 (12 versus 9)	-	-

TABLE 3 Laparoscopic myomectomy

data referring to all the study population (not only to myomectomy subgroup)

-: not stated or not assessed

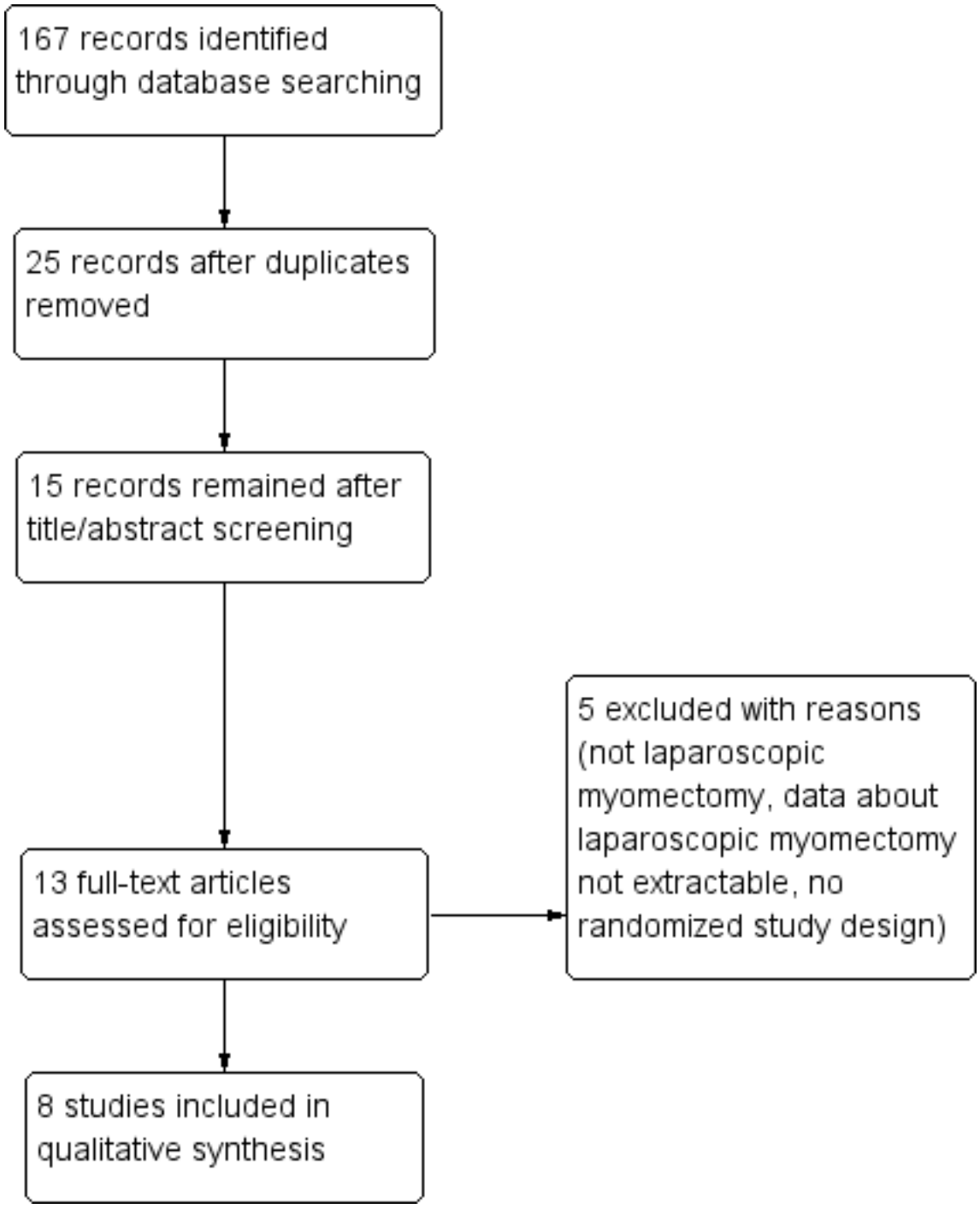
Study	Time to 2nd look surgery (days) [treatment vs control group]	Patients with adhesion at 2nd look surgery		Total score at 2nd look surgery		Uterine score at 2nd look surgery		Uterine score at 2nd look surgery versus baseline	
		Treatment vs control group (%)	p	Treatment vs control group (%)	p	Treatment vs control group (%)	p	Treatment vs control group (%)	p
1995 Mais	84 to 98	32 (64.0) [10 (40) vs 22 (88)]	<0.05	1.3 ± 0.5 vs 1.9 ± 0.8	0.0026	-	-	-	-
2003 Pellicano	60 to 90	19 (52.8) [5 (27.8) vs 14 (77.8)]	0.01	-	-	-	-	-	-
2006 Mais	91 ± 28 vs 78 ± 37	21 (48.8) [8 (38.1) vs 13 (59.1)]	ns	2.1 ± 3.9 vs 2.1 ± 2.2	ns	0.6 ± 0.9 vs 0.9 ± 1.0	ns	0.3 ± 0.9 vs 0.8 ± 1.0	0.03
2011 Trew	56.4 ± 25.2 vs 59.0 ± 37.4	-		8.13 ± 12.37 vs 8.42 ± 11.80	ns	Posterior uterus: 2.71 ± 2.04 vs 5.04 ± 4.13	**0.007**	-	-
						Anterior uterus: 3.83 ± 3.43 vs 4.17 ± 2.23	ns		
2011 Tinelli	949 ± 73 vs 912.5 ± 292	53 (19.3) [22 (15.9) vs 31 (22.6)]	ns	1.8 ± 0.8 vs 2.1 ± 0.8	0.0021	-	-	-	-
2011 Fossum	21 to 84	6 (14.6) [1 (4.8) vs 5 (25.0)]	ns	-	-	-	-	0.68 vs 1.56	-
2014 Tchartchian	65.6 ± 6.8 vs 66.6 ± 7.0	7 (46.7) [6 (75) vs 1 (12.5)]	ns	-	-	Severity score of sites adherent to the uterus: 1.63 ± 1.06 vs 0.8 ± 1.1	ns	-	-

						Extent of sites adherent to the uterus: 0.92 ± 0.66 vs 0.6 ± 0.89	ns		
						Area of sites adherent to the uterus in cm^2: 2.19 ± 2.32 vs 2.7 ± 5.24	ns		
2017 Trew	28 to 64	-		1.54 ± 1.32 vs 2.74 ± 1.36	**0.010**	(Posterior uterus) 1.61 ± 1.38 vs 2.56 ± 1.71	0.058	1.28 ± 1.56 vs 2.38 ± 1.82	0.068

TABLE 4 Second-look surgery

ns: not significant

-: not stated or not assessed



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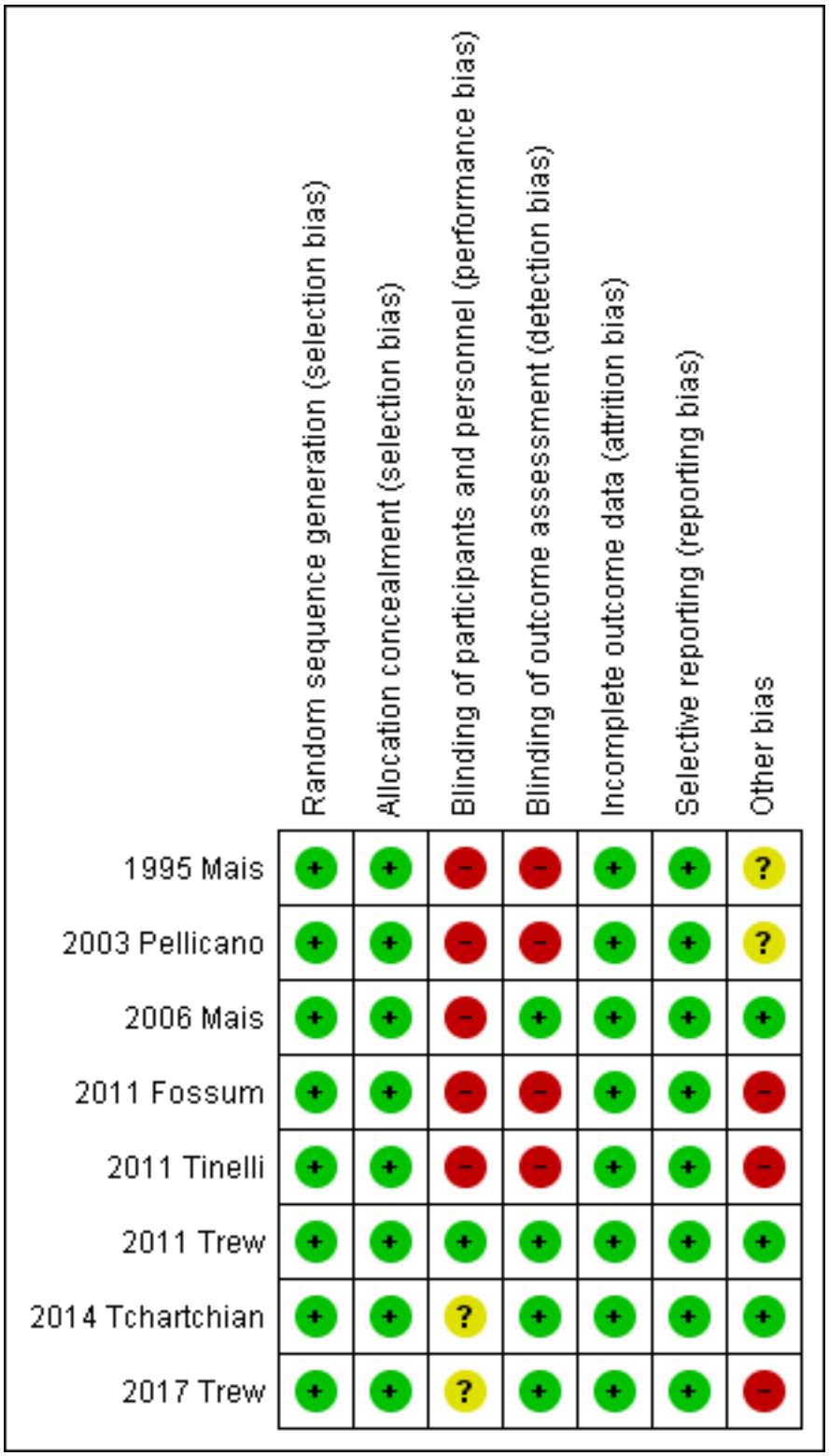

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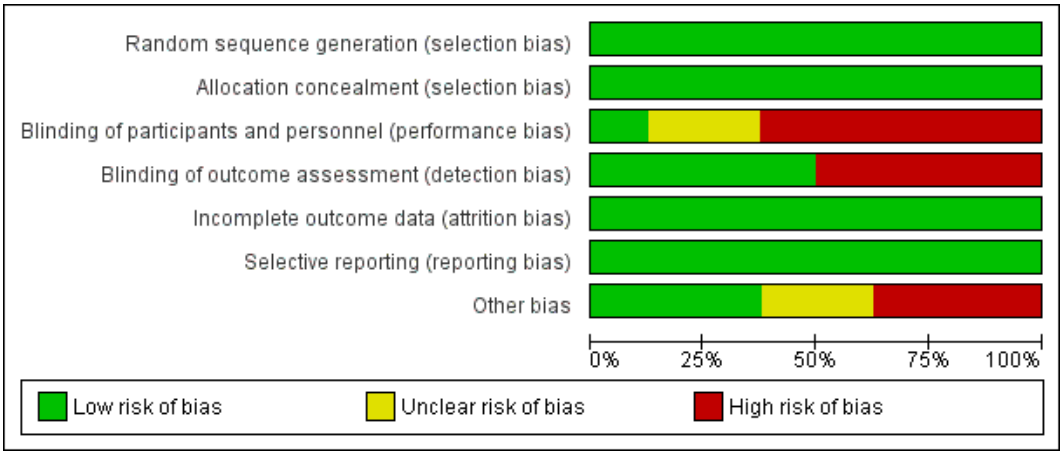

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