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## Barrier agents for adhesion prevention after gynaecological surgery (Review)

Ahmad G, Kim K, Thompson M, Agarwal P, O'Flynn H, Hindocha A, Watson A

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[Intervention Review]

# Barrier agents for adhesion prevention after gynaecological surgery

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## ABSTRACT

### Background

Pelvic adhesions can form secondary to inflammation, endometriosis, or surgical trauma. Strategies to reduce pelvic adhesion formation include placing barrier agents such as oxidised regenerated cellulose, polytetrafluoroethylene, and fibrin or collagen sheets between pelvic structures.

### Objectives

To evaluate the effects of barrier agents used during pelvic surgery on rates of pain, live birth, and postoperative adhesions in women of reproductive age.

### Search methods

We searched the following databases in August 2019: the Cochrane Gynaecology and Fertility (CGF) Specialised Register of Controlled Trials, MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, the Cochrane Central Register of Controlled Trials (CENTRAL), Epistemonikos, and trial registries. We searched reference lists of relevant papers, conference proceedings, and grey literature sources. We contacted pharmaceutical companies for information and handsearched relevant journals and conference abstracts.

### Selection criteria

Randomised controlled trials (RCTs) on the use of barrier agents compared with other barrier agents, placebo, or no treatment for prevention of adhesions in women undergoing gynaecological surgery.

### Data collection and analysis

Three review authors independently assessed trials for eligibility and risk of bias and extracted data. We calculated odds ratios (ORs) or mean differences (MDs) with 95% confidence intervals (CIs) using a fixed-effect model. We assessed the overall quality of the evidence using GRADE (Grades of Recommendation, Assessment, Development and Evaluation) methods.

### Main results

We included 19 RCTs (1316 women). Seven RCTs randomised women; the remainder randomised pelvic organs. Laparoscopy (eight RCTs) and laparotomy (11 RCTs) were the primary surgical techniques. Indications for surgery included myomectomy (seven RCTs), ovarian surgery (five RCTs), pelvic adhesions (five RCTs), endometriosis (one RCT), and mixed gynaecological surgery (one RCT). The sole indication for surgery in three of the RCTs was infertility. Thirteen RCTs reported commercial funding; the rest did not state their source of funding.

No studies reported our primary outcomes of pelvic pain and live birth rate.

*Oxidised regenerated cellulose versus no treatment at laparoscopy or laparotomy (13 RCTs)*

At second-look laparoscopy, we are uncertain whether oxidised regenerated cellulose at laparoscopy reduced the incidence of de novo adhesions (OR 0.50, 95% CI 0.30 to 0.83, 3 RCTs, 360 participants;  $I^2 = 75%$ ; very low-quality evidence) or of re-formed adhesions (OR 0.17, 95% CI 0.07 to 0.41, 3 RCTs, 100 participants;  $I^2 = 36%$ ; very low-quality evidence).

At second-look laparoscopy, we are uncertain whether oxidised regenerated cellulose affected the incidence of de novo adhesions after laparotomy (OR 0.72, 95% CI 0.42 to 1.25, 1 RCT, 271 participants; very low-quality evidence). However, the incidence of re-formed adhesions may have been reduced in the intervention group (OR 0.38, 95% CI 0.27 to 0.55, 6 RCTs, 554 participants;  $I^2 = 41%$ ; low-quality evidence).

No studies reported results on pelvic pain, live birth rate, adhesion score, or clinical pregnancy rate.

*Expanded polytetrafluoroethylene versus oxidised regenerated cellulose at gynaecological surgery (two RCTs)*

We are uncertain whether expanded polytetrafluoroethylene reduced the incidence of de novo adhesions at second-look laparoscopy (OR 0.93, 95% CI 0.26 to 3.41, 38 participants; very low-quality evidence). We are also uncertain whether expanded polytetrafluoroethylene resulted in a lower adhesion score (out of 11) (MD -3.79, 95% CI -5.12 to -2.46, 62 participants; very low-quality evidence) or a lower risk of re-formed adhesions (OR 0.13, 95% CI 0.02 to 0.80, 23 participants; very low-quality evidence) when compared with oxidised regenerated cellulose.

No studies reported results regarding pelvic pain, live birth rate, or clinical pregnancy rate.

*Collagen membrane with polyethylene glycol and glycerol versus no treatment at gynaecological surgery (one RCT)*

Evidence suggests that collagen membrane with polyethylene glycol and glycerol may reduce the incidence of adhesions at second-look laparoscopy (OR 0.04, 95% CI 0.00 to 0.77, 47 participants; low-quality evidence). We are uncertain whether collagen membrane with polyethylene glycol and glycerol improved clinical pregnancy rate (OR 5.69, 95% CI 1.38 to 23.48, 39 participants; very low-quality evidence).

One study reported adhesion scores but reported them as median scores rather than mean scores (median score 0.8 in the treatment group vs median score 1.2 in the control group) and therefore could not be included in the meta-analysis. The reported P value was 0.230, and no evidence suggests a difference between treatment and control groups.

No studies reported results regarding pelvic pain or live birth rate.

In total, 15 of the 19 RCTs included in this review reported adverse events. No events directly attributed to adhesion agents were reported.

### Authors' conclusions

We found no evidence on the effects of barrier agents used during pelvic surgery on pelvic pain or live birth rate in women of reproductive age because no trial reported these outcomes.

It is difficult to draw credible conclusions due to lack of evidence and the low quality of included studies. Given this caveat, low-quality evidence suggests that collagen membrane with polyethylene glycol plus glycerol may be more effective than no treatment in reducing the incidence of adhesion formation following pelvic surgery. Low-quality evidence also shows that oxidised regenerated cellulose may reduce the incidence of re-formation of adhesions when compared with no treatment at laparotomy. It is not possible to draw conclusions on the relative effectiveness of these interventions due to lack of evidence.

No adverse events directly attributed to the adhesion agents were reported. The quality of the evidence ranged from very low to moderate. Common limitations were imprecision and poor reporting of study methods. Most studies were commercially funded, and publication bias could not be ruled out.

## PLAIN LANGUAGE SUMMARY

### Barrier agents for adhesion prevention after gynaecological surgery

#### Review question

This review of trials assessed the effects of barrier agents on pelvic pain, live birth rate, clinical pregnancy rate, adhesion formation, and adhesion score (a measure of adhesion severity) after pelvic surgery.

#### Background

A common problem following pelvic surgery is the occurrence of adhesions, where the surfaces of two separate pelvic structures (e.g. inner lining of pelvic wall or pelvic organs such as uterus, ovaries, bladder, or bowel) stick together. During pelvic surgery, strategies to reduce pelvic adhesion formation include placing a synthetic physical barrier between pelvic structures.

### Study characteristics

We included 19 randomised controlled trials (RCTs) that included a total of 1316 women undergoing gynaecological surgery. These trials assessed different types of barrier agents for preventing adhesions and compared them with each other or with no treatment. The data are current to August 2019. Thirteen RCTs reported commercial funding; the other studies did not state their source of funding.

### Key results

No studies reported the effects of barrier agents used during pelvic surgery on pelvic pain or live birth rate among women of reproductive age.

Low-quality evidence suggests that oxidised regenerated cellulose and collagen membrane with polyethylene glycol plus glycerol may be more effective than no treatment in reducing the risk of adhesion formation following pelvic surgery.

One study reported the effect of collagen membrane with polyethylene glycol plus glycerol on postoperative adhesion score; however due to the way these data were reported, we are unable to interpret whether the intervention had any effect. No studies reported the effect of oxidised regenerated cellulose on adhesion score.

One study reported the effect of collagen membrane with polyethylene glycol plus glycerol on clinical pregnancy rate; however this evidence was found to be of very low quality. We are uncertain whether this intervention led to a higher clinical pregnancy rate than no treatment. No studies reported the effect of any other intervention on clinical pregnancy rate.

Two studies compared the effects of expanded polytetrafluoroethylene and oxidised regenerated cellulose on adhesion score and adhesion formation. However, this evidence was found to be of very low quality, and we are uncertain whether either intervention was more effective than the other. No studies compared the relative effects of these interventions on pelvic pain, live birth rate, or clinical pregnancy rate.

We found no conclusive evidence on the relative effectiveness of any reported interventions. No adverse events directly attributed to the adhesion agents were reported.

### Quality of the evidence

The quality of the evidence ranged from very low to moderate. The most common limitations were imprecision (few participants and wide confidence intervals) and poor reporting of study methods. Most studies were commercially funded, and publication bias could not be ruled out.

## SUMMARY OF FINDINGS

### Summary of findings for the main comparison. Analysis 1 - Oxidised regenerated cellulose vs no treatment at laparoscopy for adhesion prevention after gynaecological surgery

#### Oxidised regenerated cellulose vs no treatment at laparoscopy for adhesion prevention after gynaecological surgery

**Population:** women having gynaecological surgery  
**Settings:** surgical  
**Intervention:** oxidised regenerated cellulose (Interceed)

**Comparison:** no treatment at laparoscopy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No treatment	Oxidised regenerated cellulose				
<b>Pelvic pain</b>	Not reported in any study in this comparison					
<b>Live birth rate</b>	Not reported in any study in this comparison					
<b>Adhesion score</b>	Not reported in any study in this comparison					
<b>Incidence of adhesions - de novo</b> Incidence of adhesions at second-look laparoscopy	<b>479 per 1000</b>	<b>315 per 1000</b> (216 to 433)	<b>OR 0.50</b> (0.3 to 0.83)	360 (3 studies)	⊕○○○ <b>Very low</b> <sup>a,b,c,d</sup>	
<b>Incidence of adhesions - re-formation (or mixture)</b> Incidence of adhesions at second-look laparoscopy	<b>746 per 1000</b>	<b>333 per 1000</b> (171 to 546)	<b>OR 0.17</b> (0.07 to 0.41)	100 (3 studies)	⊕○○○ <b>Very Low</b> <sup>a,c,d</sup>	
<b>Clinical pregnancy rate</b>	Not reported in any study in this comparison					

\*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  
 CI: confidence interval; OR: odds ratio.

GRADE Working Group grades of evidence.

**High quality:** further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.  
**Very low quality:** we are very uncertain about the estimate.

<sup>a</sup>Downgraded one level due to risk of bias; high level of attrition in one study.

<sup>b</sup>Downgraded one level due to inconsistency;  $I^2 = 75\%$ .

<sup>c</sup>Downgraded one level due to unclear risk of publication bias.

<sup>d</sup>Downgraded one level due to imprecision: small number of events and relatively wide confidence intervals.

## Summary of findings 2. Analysis 2 - Oxidised regenerated cellulose vs no treatment at laparotomy for adhesion prevention after gynaecological surgery

### Oxidised regenerated cellulose vs no treatment at laparotomy for adhesion prevention after gynaecological surgery

**Population:** women having gynaecological surgery

**Settings:** surgical

**Intervention:** oxidised regenerated cellulose

**Comparison:** no treatment at laparotomy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No treatment	Oxidised regenerated cellulose				
<b>Pelvic pain</b>	Not reported in any study in this comparison					
<b>Live birth rate</b>	Not reported in any study in this comparison					
<b>Adhesion score</b>	Not reported in any study in this comparison					
<b>Incidence of adhesions - de novo</b> Incidence at second-look laparoscopy	<b>479 per 1000</b>	<b>399 per 1000</b> (279 to 535)	<b>OR 0.72</b> (0.42 to 1.25)	271 (1 study)	⊕⊕⊕⊕ <b>Very Low</b> <sup>a,b,c</sup>	
<b>Incidence of adhesions - re-formation (or mixture)</b> Incidence at second-look laparoscopy	<b>746 per 1000</b>	<b>528 per 1000</b> (443 to 618)	<b>OR 0.38</b> (0.27 to 0.55)	554 (6 studies)	⊕⊕⊕⊕ <b>Low</b> <sup>c,d</sup>	
<b>Clinical pregnancy rate</b>	Not reported in any study in this comparison					

\*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; OR: odds ratio.

GRADE Working Group grades of evidence.

**High quality:** further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** we are very uncertain about the estimate.

<sup>a</sup>Downgraded one level due to risk of bias; high level of attrition in one study.

<sup>b</sup>Downgraded one level due to imprecision: small number of events and wide confidence intervals.

<sup>c</sup>Downgraded one level due to unclear risk of publication bias.

<sup>d</sup>Downgraded one level due to inconsistency: moderate heterogeneity ( $I^2 = 41\%$ ).

### Summary of findings 3. Analysis 4 - Expanded polytetrafluoroethylene vs oxidised regenerated cellulose for adhesion prevention after gynaecological surgery

#### Expanded polytetrafluoroethylene vs oxidised regenerated cellulose (Interceed) for adhesion prevention after gynaecological surgery

**Population:** women having gynaecological surgery

**Settings:** surgical

**Intervention:** expanded polytetrafluoroethylene

**Comparison:** oxidised regenerated cellulose

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Oxidised regenerated cellulose	Expanded polytetrafluoroethylene				
<b>Pelvic pain</b>	Not reported in any study in this comparison					
<b>Live birth rate</b>	Not reported in any study in this comparison					
<b>Adhesion score</b> Non-validated score out of 11 at SLL	Mean adhesion score was <b>-3.79 lower</b> (5.12 to 2.46 lower) in the expanded polytetrafluoroethylene group			58 (1 study)	⊕⊕⊕⊕ <b>Very low</b> <sup>a,b,c</sup>	
<b>Incidence of adhesions - de novo</b> Incidence at second-look laparoscopy	<b>149 per 1000</b>	<b>141 per 1000</b> (44 to 374)	<b>OR 0.93</b> (0.26 to 3.41)	38 (1 study)	⊕⊕⊕⊕ <b>Very low</b> <sup>c,d</sup>	



<b>Incidence of adhesions - re-formation (or mixture)</b> Incidence at second-look laparoscopy	<b>567 per 1000</b>	<b>146 per 1000</b> (26 to 512)	<b>OR 0.13</b> (0.02 to 0.8)	23 (1 study)	⊕⊕⊕⊕ <b>Very low</b> <sup>c,d</sup>	Confidence interval crossed the line of no effect when a risk ratio rather than an odds ratio was calculated (RR 0.36, 95% CI 0.13 to 1.01)
<b>Clinical pregnancy rate</b>	Not reported in any study in this comparison					

\*The basis for the **assumed risk** is the median oxidised regenerated cellulose group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  
CI: confidence interval; OR: odds ratio; RR: risk ratio.

GRADE Working Group grades of evidence.

**High quality:** further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** we are very uncertain about the estimate.

<sup>a</sup>Downgraded one level due to imprecision: small number of events and wide confidence intervals.

<sup>b</sup>Downgraded one level due to risk of bias: non-validated adhesion scoring system used.

<sup>c</sup>Downgraded one level due to unclear risk of publication bias.

<sup>d</sup>Downgraded two levels due to imprecision: small number of events and wide confidence intervals which cross the line of no effect.

#### Summary of findings 4. Analysis 7 - Collagen membrane with polyethylene glycol and glycerol vs Ringer's lactate

##### Collagen membrane with polyethylene glycol and glycerol vs Ringer's lactate

**Patient or population:** patients with adhesion prevention after gynaecological surgery

**Settings:** surgical

**Intervention:** collagen membrane with polyethylene glycol and glycerol

**Comparison:** Ringer's lactate

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				



	Ringer's lactate	Collagen membrane with poly-ethylene glycol and glycerol			
<b>Pelvic pain</b>	Not reported in any study in this comparison				
<b>Live birth rate</b>	Not reported in any study in this comparison				
<b>Adhesion score</b>	Median adhesion score in the control group was 0.8 compared with 1.2 in the intervention group		47 (1 study)	⊕⊕⊕⊕	<b>Very low</b> <sup>a,b,c</sup>
<b>Incidence of adhesions - de novo</b>	<b>479 per 1000</b>	<b>36 per 1000</b> (0 to 415)	<b>OR 0.04</b> (0.00 to 0.77)	47 (1 study)	⊕⊕⊕⊕ <b>Low</b> <sup>a,c</sup>
Incidence at second-look laparoscopy					
<b>Incidence of adhesions - re-formation or mixture</b>	Not reported in any study in this comparison				
Incidence at second-look laparoscopy					
<b>Clinical pregnancy rate</b>	<b>235 per 1000</b>	<b>637 per 1000</b> (298 to 879)	<b>OR 5.69</b> (1.38 to 23.48)	39 (1 study)	⊕⊕⊕⊕ <b>Very low</b> <sup>a,c,d</sup>

\*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).  
CI: confidence interval; OR: odds ratio.

GRADE Working Group grades of evidence.

**High quality:** further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** we are very uncertain about the estimate.

<sup>a</sup>Downgraded one level due to imprecision: small sample size and wide confidence intervals.

<sup>b</sup>Downgraded one level due to risk of bias: adhesion scores reported as median (min-max) rather than mean and standard deviation.

<sup>c</sup>Downgraded one level due to unclear risk of publication bias.

<sup>d</sup>Downgraded one level due to risk of bias: high level of attrition.

## BACKGROUND

### Description of the condition

Pelvic adhesions can form as the result of pelvic inflammation, endometriosis, or surgical trauma. The incidence of pelvic adhesions at second-look laparoscopy in the first few weeks after surgery has been reported to be between 25% and 92% (Okabayashi 2014). Consequences of adhesion formation include subfertility, development of chronic abdominal pain, and dyspareunia (difficult or painful sexual intercourse) (SRS 2007). A recent study demonstrated that in women with a known reason for small-bowel obstruction, adhesions were the single most common cause (Ten Broek 2013).

Cutting, surgical denudation, ischaemia, desiccation, or abrasion can cause peritoneal trauma during surgery. Subsequent healing in the peritoneal cavity occurs through a combination of mesothelial regeneration and fibrosis, resulting in adhesion formation between damaged serosal surfaces (diZerega 1990).

Minimally invasive techniques such as laparoscopy reduce the risk of de novo (new) adhesion formation but do not eliminate it entirely. Studies included within this review therefore assessed both laparoscopy and laparotomy.

### Description of the intervention

Several barrier agents with different characteristics are commercially available. Oxidised regenerated cellulose was the first tested synthetic mechanical barrier agent to cover traumatised peritoneum in the pelvis. It is applied over raw tissue surfaces at the last stage of surgery after haemostasis has been achieved, and it is designed to form a gelatinous protective coat within eight hours of application. Following this, it is broken down into its monosaccharide constituents and is designed to be absorbed within two weeks. Concerns with use of oxidised regenerated cellulose include migration and the need for meticulous haemostasis. Use of oxidised regenerated cellulose in the presence of bleeding may promote fibrin deposition at sites of incomplete haemostasis, resulting in adhesion formation rather than prevention (Wiseman 1999).

Another commercially available barrier agent is expanded polytetrafluoroethylene surgical membrane. This inert and permanent barrier acts by preventing cellular growth. However, it must be sutured to remain in place, and this may increase the incidence of adhesions while prolonging operating time. Much debate is ongoing regarding the need to remove expanded polytetrafluoroethylene after peritoneal healing is complete. This debate stems from studies investigating expanded polytetrafluoroethylene in vascular and pericardial grafts, which found no significant long-term adverse effects when the barrier was not removed (Jacobs 1996). In addition, a prospective multi-centre observational study investigating the long-term use of expanded polytetrafluoroethylene without removal reported only one case of postoperative infection, which did not require removal of the membrane (Hurst 1998).

Other products include sodium hyaluronate with carboxymethylcellulose, an adhesion barrier agent composed of chemically derived sodium hyaluronate and carboxymethylcellulose. It is designed to be absorbed from the peritoneal cavity within seven days and completely excreted from

the body within 28 days (Diamond 1996). Sodium hyaluronate with carboxymethylcellulose consists of chemically modified hyaluronic acid and carboxymethylcellulose. It separates denuded planes of tissue for up to seven days before it is absorbed. As with oxidised regenerated cellulose, migration is the cause of some concern; however no evidence suggests that its effectiveness is altered by the presence of blood. Although evidence for its use in gynaecological surgery is limited, sodium hyaluronate with carboxymethylcellulose has been widely studied in the context of colorectal surgery. Formation of adhesions and incidence of small-bowel obstruction were reduced in five randomised controlled trials (RCTs) investigating its use in various colorectal and general surgical procedures (Ten Broek 2013).

Another product is a dual-sided hydrophilic film. One side is a smooth surface consisting of porcine collagen, polyethylene glycol, and glycerol, and the opposite side is a porous surface made of lyophilised porcine collagen. The film is designed to degrade in the body within three weeks of application, and it has demonstrated significant reduction in adhesion formation in rat models (Gruber-Blum 2011).

Fibrin sheet is a sheet-type fibrin sealant with a solid layer of human fibrinogen, thrombin, and aprotinin coating the active surface of equine collagen stained with riboflavin (Mais 1995a; Pellicno 2003).

Fluid and pharmacological methods used to prevent adhesion formation are investigated in another Cochrane Review (Ahmad 2014).

### How the intervention might work

Theoretically, inert physical materials that are able to prevent mechanical contact between serosal surfaces for longer than three days have the potential to be helpful in preventing adhesion formation. This would allow independent healing of each traumatised peritoneal surface. Some barrier agents (e.g. expanded polytetrafluoroethylene) need to be sutured into place, requiring extra operating time, especially during laparoscopic procedures.

### Why it is important to do this review

This review is concerned with the effectiveness of barrier agents placed in the peritoneal cavity for preventing adhesions and in some cases for improving fertility. Pharmacological adjuncts are reviewed elsewhere. Women present with the secondary effects of adhesions, including dyspareunia, subfertility, bowel obstruction, and chronic pelvic pain. These problems can greatly impact quality of life and may necessitate further surgery. No clinical consensus or guidance is available regarding the most effective anti-adhesion agent. Assessment of the evidence on effectiveness of barrier agents is therefore important.

## OBJECTIVES

To evaluate the effects of barrier agents used during pelvic surgery on rates of pain, live birth, and postoperative adhesions in women of reproductive age.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included published or unpublished randomised controlled trials (RCTs) in which either women or pelvic structures were the unit of randomisation. Non-randomised studies (e.g. studies with evidence of inadequate sequence generation such as alternate days or participant numbers) were excluded, as they are associated with high risk of bias. In the case of cross-over trials, only data from before the cross-over would have been included, as any additional pelvic surgery increases the risk of adhesion formation. However, no cross-over trials were identified.

#### Types of participants

Women undergoing pelvic surgery for infertility or for other indications. Studies investigating adhesion prevention in non-gynaecological specialties were excluded. Types of surgery performed could include open or laparoscopic procedures.

#### Types of interventions

Trials comparing physical barrier agents (oxidised regenerated cellulose, expanded polytetrafluoroethylene, sodium hyaluronate with carboxymethylcellulose, fibrin sheet, collagen membrane with polyethylene glycol and glycerol) used during pelvic surgery versus any other physical barrier agent or placebo or no treatment were included.

Studies of fibrin glue and Sepracoat (Genzyme Corporation) were excluded, as these are not physical barrier agents.

#### Types of outcome measures

##### Primary outcomes

1. Pelvic pain (improvement/worsening/no change in pain at second-look laparoscopy (SLL)), as measured by validated pain scales, for example, visual analogue pain scale (VAS) scores, the McGill Pain Questionnaire (MPQ), a pain improvement rating scale, general pain experience, or a gynaecological pain questionnaire
2. Live birth rate

##### Secondary outcomes

1. Adhesion score, recorded on whichever scale the study authors used but with preference given to the modified American Fertility Society (mAFS) score
2. Number of participants with adhesions at SLL
3. Clinical pregnancy rate (pregnancy confirmed on ultrasound scan)
4. Miscarriage rate, defined as loss of pregnancy before 24 weeks of gestation
5. Ectopic pregnancy rate
6. Number of participants with improvement in quality of life (QoL) at SLL, recorded on whichever scale was chosen by study authors
7. Adverse events

Live birth rate and clinical pregnancy rate are relevant when studies have specifically investigated use of the barrier agent in procedures performed to improve fertility. This does not apply to some studies.

Articles that met the inclusion criteria but did not report any of the outcomes considered within this review were also included within the qualitative analysis.

#### Search methods for identification of studies

We searched for all published and unpublished RCTs comparing the use of barrier agents versus any other active intervention or placebo/no treatment without language restriction. Searches were designed and conducted by the Information Specialist for Cochrane Gynaecology and Fertility.

#### Electronic searches

We searched:

1. Cochrane Gynaecology and Fertility Group (CGFG) Specialised Register of Controlled Trials; Procite platform, searched 21 August 2019 ([Appendix 1](#));
2. Central Register of Controlled Trials (CENTRAL); OVID platform, searched 21 August 2019 ([Appendix 2](#));
3. MEDLINE; OVID platform, searched from 1946 to 21 August 2019 ([Appendix 3](#));
4. Embase; OVID platform, searched from 1980 to 21 August 2019 ([Appendix 4](#)); and
5. PsycINFO; OVID platform, searched from 1806 to 21 August 2019 ([Appendix 5](#)).

These searches were conducted by the Information Specialist for the Cochrane Gynaecology and Fertility Group.

Other electronic searches included trial registers for the US National Institutes of Health, the World Health Organization (WHO) international trial registry platform, the Database of Abstracts of Reviews of Effects (DARE), OpenGrey, PubMed, Epistemonikos, and Google Scholar.

We conducted the last search in August 2019.

#### Searching other resources

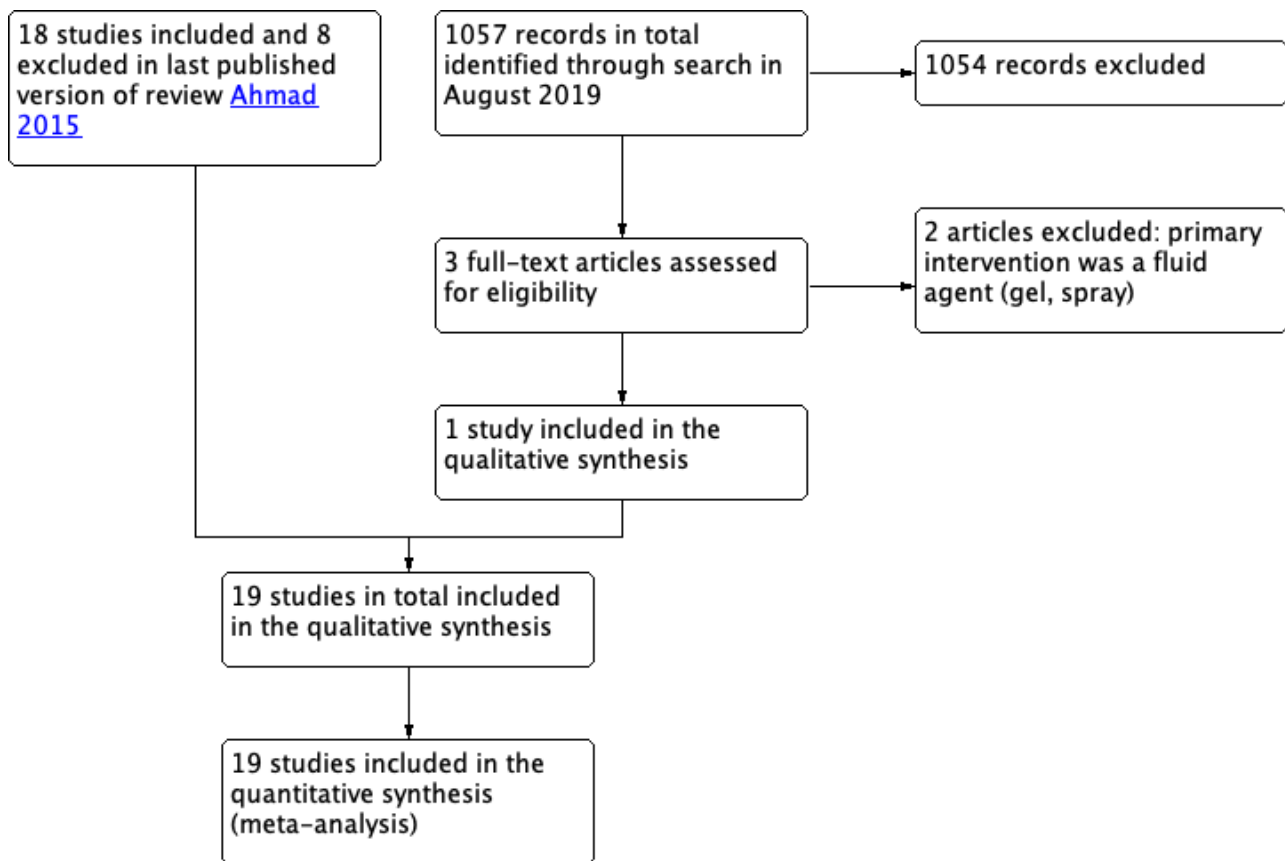
We also searched the reference lists of relevant publications, review articles, and included studies and contacted experts in the field to request additional data. We handsearched relevant journals and conference abstracts that were not covered in the CGF register, in liaison with the Information Specialist. Two review authors screened retrievals.

#### Data collection and analysis

##### Selection of studies

After an initial screen of titles and abstracts identified by the search, we retrieved the full text of all potentially eligible studies. Three review authors (PA, KK, MT) independently examined these full-text articles for compliance with inclusion criteria. Disagreements on study eligibility were resolved by consultation with a fourth review author (GA). Review authors corresponded with study investigators to clarify study eligibility (e.g. with respect to participant eligibility criteria and allocation method). [Figure 1](#) shows a flow diagram of study selection.

**Figure 1. Study flow diagram.**



**Data extraction and management**

Three review authors (PA, KK, MT) independently extracted data from eligible studies using a data extraction form that was designed and pilot-tested by the review authors. Disagreements were resolved by consultation with a fourth review author (GA). Data extracted included study characteristics and outcome data. When studies were followed by multiple publications, the main trial report was used as the reference, and additional details were derived from secondary papers. We corresponded with study investigators to ask for further data on methods and/or results, as required.

**Assessment of risk of bias in included studies**

We assessed each included trial for the following criteria using the Cochrane risk of bias assessment tool: sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; completeness of outcome data; selective outcome reporting; and other potential sources of bias (Higgins 2011). We presented conclusions in the 'Risk of bias' table and incorporated them into the interpretation of review findings by performing sensitivity analyses. Two review authors (KK, MT) independently performed all assessments of the quality of clinical trials. All discrepancies were resolved by GA and PA.

Care was taken to search for within-study reporting bias, as seen in trials failing to report obvious outcomes (e.g. pregnancy rate, major complications) or reporting them in insufficient detail.

**Measures of treatment effect**

Results of dichotomous variables are presented as Mantel-Haenszel odds ratios (ORs) with 95% confidence intervals (CIs), and results of continuous variables are presented as mean differences (MDs).

We reversed the direction of effects of individual studies, when required, to ensure consistency across trials. We treated ordinal data as continuous outcomes. We presented 95% CIs for all outcomes. When data used to calculate ORs or MDs were not available, we planned to utilise the most detailed numerical data available, which might facilitate similar analyses of included studies. We compared the magnitude and direction of effects reported by studies versus how they are presented in the review, taking account of legitimate differences.

**Unit of analysis issues**

For within-participant designs, 'effective sample sizes' were calculated to allow for statistical synthesis, that is, for a trial randomly assigning ovaries within each participant rather than randomly assigning participants, numbers were calculated to simulate as nearly as possible the odds ratio and the confidence interval as if the study design had randomly assigned participants, not ovaries. This was achieved as follows.

1. We calculated the odds ratio and the 95% CI for the matched design.

2. We constrained the control rate in the hypothetical parallel design to make it equal to that observed in the matched design.
3. We constrained group sizes for the parallel design to make them equal to each other.
4. Based on the two constraints above, we calculated the numbers of 'successes' and 'failures' in each group to reproduce as nearly as possible the OR (95% CI) of the matched design.

As a result of this type of re-analysis of data, studies with within-participant design that may have previously demonstrated significance may no longer do so.

Several studies of within-participant design comparing oxidised regenerated cellulose versus no treatment were presented and analysed wrongly as having a parallel design. We recognised that failure to account for pairing and failure to take account of doubling the sample size by using ovaries instead of participants as the unit of randomisation may have yielded spurious results. For these studies, the least favourable outcome for oxidised regenerated cellulose that was compatible with the reported results was assumed. We attempted to obtain correct results tables from study authors but were unsuccessful.

#### Dealing with missing data

Data were analysed on an intention-to-treat (ITT) basis as far as possible, and attempts were made to obtain missing data from the original investigators. When data for primary outcomes could not be obtained, we planned to undertake imputation of individual values. For secondary outcomes, only available data were analysed.

If studies reported sufficient detail to calculate mean differences but no information on associated standard deviation (SD), we assumed that the outcome had a standard deviation equal to the highest SD from other studies within the same analysis.

#### Assessment of heterogeneity

Clinical and methodological characteristics of individual studies were considered to ensure that any pooling was clinically meaningful. The  $I^2$  statistic was calculated to assess statistical heterogeneity. An  $I^2$  measurement over 50% was taken to indicate substantial heterogeneity.

#### Assessment of reporting biases

In view of the difficulties involved in detecting and correcting publication bias and other reporting biases, study authors aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies, and by remaining alert for duplication of data. We aimed to minimise the impact by ensuring that a robust and comprehensive search was performed. We planned to create a funnel plot of 10 or more studies that were included in a meta-analysis to explore the possibility of small-study effects (a tendency for estimates of the intervention effect to suggest that it is more beneficial in smaller studies).

#### Data synthesis

Statistical analysis was performed in accordance with the guidelines developed by Cochrane. Data from the primary studies were combined in RevMan using the fixed-effect model. We planned to report standardised mean differences (SMDs) if similar outcomes

were reported on different scales. An increase in OR, SMD, or MD was indicated to the right of the central line of the forest plot, and a decrease was indicated to the left of the central line. Whether this favoured treatment or no treatment depended on the outcome analysed, but the axes were labelled accordingly. Analyses were stratified by type of barrier agent, type of surgery, and type of control.

#### Subgroup analysis and investigation of heterogeneity

If we had detected substantial heterogeneity, we planned to explore possible explanations via sensitivity analyses. We planned to take any statistical heterogeneity into account when interpreting the results, especially if any variation in the direction of effect was evident.

#### Sensitivity analysis

We conducted sensitivity analyses for the important review outcomes to determine whether the conclusions were robust to arbitrary decisions made regarding eligibility of studies and analysis. These analyses included consideration of whether review conclusions differed if:

1. eligibility was restricted to studies without high risk of bias;
2. a random-effects model had been adopted; or
3. relative risk had been used as the summary effects measure.

#### Overall quality of the body of evidence: 'Summary of findings' table

We prepared 'Summary of findings' tables using GRADEpro software and Cochrane methods ([GRADEpro GDT 2015](#); [Higgins 2011](#)). These tables evaluate the overall quality of the body of evidence for the main review outcomes (pelvic pain, live birth rate, clinical pregnancy rate, improvement or worsening of adhesion scores, and incidence of adhesions) using GRADE (Grades of Recommendation, Assessment, Development and Evaluation) criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness, and publication bias). Judgements about evidence quality (high, moderate, or low) have been justified, documented, and incorporated into reporting of results for each outcome.

## RESULTS

### Description of studies

#### Results of the search

At the 2020 update three studies were retrieved in full text. One new study was identified and was included within the meta-analysis in this update ([Canis 2014](#)), and two were excluded; there are now 19 included studies and 10 excluded. See [Figure 1](#) for an overview of search results.

At the 2015 update eighteen studies met inclusion criteria, and eight studies were excluded. See study tables under [Characteristics of included studies](#). Reasons why studies were excluded are detailed in the [Characteristics of excluded studies](#) tables.



## Included studies

### *Trial design and setting*

#### Number of studies

We identified 19 RCTs that met the inclusion criteria (1309 participants).

#### Multi-centre trials

Ten were multi-centre studies (Azziz 1993; Canis 2014; Diamond 1996; Franklin 1995; Haney 1995; Myomectomy ASG 1995; Nordic APSG 1995; Sekiba 1992; Takeuchi 2005; Tinelli 2011).

#### Design

In seven parallel-group trials, the unit of randomisation was the participant (Canis 2014; Diamond 1996; Mais 1995a; Mais 1995b; Takeuchi 2005; Tinelli 2011; Wallweiner 1998). The remainder were within-participant trials in which the unit of randomisation was the ovary, uterine sites, or the pelvic sidewall. One study was a multi-arm trial comparing fibrin gel and a fibrin sheet versus control (Takeuchi 2005). Comparison of the fibrin sheet arm versus the control arm is included in this review.

#### Support/sponsorship

Thirteen trials stated sponsorship. Seven trials were sponsored by Johnson & Johnson (Azziz 1993; Franklin 1995; Li 1994; Nordic APSG 1995; Saravelos 1996; Sekiba 1992; van Geldorp 1994), one was sponsored by Genzyme (Diamond 1996), one by Covidien (Canis 2014), and a further two trials by manufacturers of expanded polytetrafluoroethylene (Haney 1995; Myomectomy ASG 1995). One trial received additional sponsorship from the Medical Research Council (MRC) in Canada (Greenblatt 1993). Another trial received support from Johnson & Johnson after the study was completed to help with the analysis, but the final content of the paper was under the sole control of the principal investigator (Keckstein 1996).

#### Participants

##### Primary indications for surgery

Myomectomy was the indication in six trials (Canis 2014; Diamond 1996; Mais 1995b; Myomectomy ASG 1995; Takeuchi 2005; Tinelli 2011), and ovarian surgery was the indication in four trials (Greenblatt 1993; Keckstein 1996; Saravelos 1996; van Geldorp 1994). Three trials were restricted to women undergoing adhesiolysis for infertility (Azziz 1993; Nordic APSG 1995; Sekiba 1992). Participants also underwent adhesiolysis in Li 1994, although the indications were subgrouped into infertility or pelvic pain. The indication for the Haney 1995 trial was also pelvic adhesions, although the primary reason for surgery was not exclusively infertility, and this trial was not subgrouped. The indications were endometriosis in Mais 1995a and Wallweiner 1998, and bilateral ovarian disease in Franklin 1995.

##### Type of surgery

Laparotomy was performed in nine trials (Azziz 1993; Canis 2014; Diamond 1996; Franklin 1995; Li 1994; Myomectomy ASG 1995; Nordic APSG 1995; Sekiba 1992; van Geldorp 1994), and laparoscopy was performed in the remainder (Greenblatt 1993; Haney 1995; Keckstein 1996; Korell 1994; Mais 1995a; Mais 1995b; Saravelos 1996; Takeuchi 2005; Wallweiner 1998). Tinelli 2011 performed both laparoscopy and laparotomy.

## Suturing

Oxidised regenerated cellulose was occasionally sutured into place (Keckstein 1996; Li 1994; Sekiba 1992), whereas expanded polytetrafluoroethylene was always sutured into place (Haney 1995; Korell 1994; Myomectomy ASG 1995).

### Adjuvants to surgery

One trial compared oxidised regenerated cellulose versus no treatment; hydrocortisone was also instilled in both treatment and control groups (Li 1994).

### Microsurgical techniques

In three trials, it was noted that microsurgery was performed (Azziz 1993; Li 1994; Nordic APSG 1995).

## Interventions

1. Thirteen RCTs compared oxidised regenerated cellulose with no treatment - six at laparoscopy (Keckstein 1996; Mais 1995a; Mais 1995b; Saravelos 1996; Tinelli 2011; Wallweiner 1998), and seven at laparotomy (Azziz 1993; Franklin 1995; Li 1994; Nordic APSG 1995; Sekiba 1992; Tinelli 2011; van Geldorp 1994)
2. Two RCTs compared expanded polytetrafluoroethylene versus oxidised regenerated cellulose (Haney 1995; Korell 1994)
3. One RCT compared expanded polytetrafluoroethylene versus no treatment (Myomectomy ASG 1995)
4. One RCT compared sodium hyaluronate with carboxymethylcellulose versus no treatment (Diamond 1996)
5. One RCT compared fibrin sheet versus no treatment (Takeuchi 2005)
6. One RCT compared collagen film with polyethylene glycol and glycerol versus Ringer's lactate (Canis 2014)

### Timing of second-look laparoscopy (SLL)

Only two studies stated a mean time after laparoscopy (Diamond 1996 - 23 days; Haney 1995 - 30 days). Large variation was noted in timing of the SLL both within and between studies. Only three studies performed all SLL procedures within six weeks (Greenblatt 1993; Haney 1995; Myomectomy ASG 1995). Only four further studies performed SLL after eight weeks (Keckstein 1996; Mais 1995a; Mais 1995b; Wallweiner 1998). Remaining studies performed SLL after 10 days to 20 weeks.

Tinelli 2011 did not routinely perform SLL but instructed participants to have any further surgery completed within a six-year period. Adhesions were assessed at the second surgery. Timing of the second surgery varied between 2.3 and 2.5 years.

## Studied outcomes

### Primary outcomes

#### Pelvic pain

No trials reported this outcome.

#### Live birth rate

No trials reported this outcome.

**Secondary outcomes**

**Adhesion score**

Only one study reported mean adhesion score as an outcome (Haney 1995). Another study reported median adhesion score as an outcome (Canis 2014).

**Number of participants with adhesions at SLL**

Nine trials reported the incidence of de novo adhesions as an outcome (Canis 2014; Diamond 1996; Greenblatt 1993; Korell 1994; Mais 1995b; Myomectomy ASG 1995; Saravelos 1996; Takeuchi 2005; Tinelli 2011). Ten trials reported the incidence of re-formation adhesions as an outcome (Azziz 1993; Franklin 1995; Haney 1995; Keckstein 1996; Li 1994; Mais 1995a; Nordic APSG 1995; Sekiba 1992; van Geldorp 1994; Wallweiner 1998).

**Clinical pregnancy rate**

One study reported this outcome (Canis 2014).

**Miscarriage rate**

No trials reported this outcome.

**Ectopic pregnancy rate**

One study reported this outcome (Canis 2014).

**Quality of life**

No trials reported this outcome.

**Adverse effects**

Fourteen studies reported adverse effects as an outcome (Azziz 1993; Canis 2014; Diamond 1996; Franklin 1995; Haney 1995; Keckstein 1996; Mais 1995a; Mais 1995b; Myomectomy ASG 1995; Nordic APSG 1995; Saravelos 1996; Takeuchi 2005; Tinelli 2011; van Geldorp 1994). In the remaining studies, the absence of adverse effects was not stated.

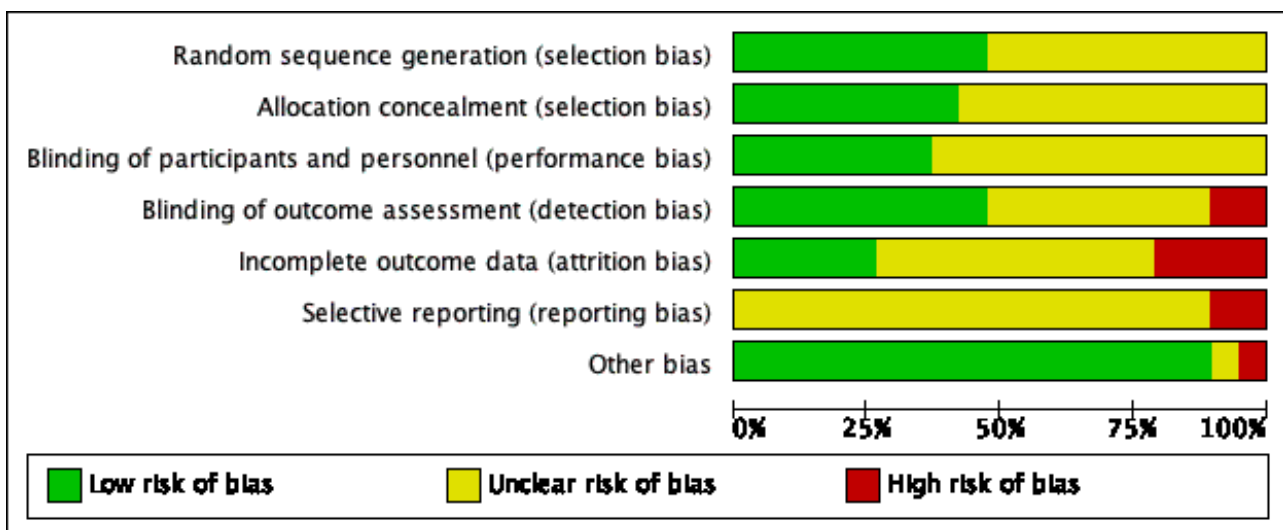
**Excluded studies**

Ten studies were excluded. In nine studies, the agent used as the intervention was not a barrier agent, and one study did not investigate use of a barrier agent during a gynaecological procedure (To 1992).

**Risk of bias in included studies**

See Figure 2 and Figure 3 for a summary diagram.

**Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**





**Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
<b>Azziz 1993</b>	?	?	+	-	-	?	+
<b>Cants 2014</b>	+	+	+	+	-	?	+
<b>Diamond 1996</b>	+	+	+	+	+	?	+
<b>Franklin 1995</b>	?	?	+	?	+	?	+
<b>Greenblatt 1993</b>	?	?	?	+	+	?	-
<b>Haney 1995</b>	+	+	+	-	?	?	+
<b>Keckstein 1996</b>	+	+	+	?	-	?	+
<b>Korell 1994</b>	?	?	?	?	?	?	+
<b>Li 1994</b>	?	+	+	+	+	-	?
<b>Mals 1995a</b>	+	+	?	+	?	?	+
<b>Mals 1995b</b>	+	+	?	+	?	?	+
<b>Myomectomy ASG 1995</b>	+	+	?	?	+	?	+
<b>Nordic APSG 1995</b>	?	?	?	?	?	-	+
<b>Saravelos 1996</b>	?	?	?	+	?	?	+
<b>Sekiba 1992</b>	?	?	?	+	?	?	+
<b>Takeuchi 2005</b>	+	?	?	?	?	?	+
<b>Tinelli 2011</b>	+	?	?	+	-	?	+
<b>van Geldorp 1994</b>	?	?	?	?	?	?	+
<b>Walker 1998</b>	?	?	?	?	?	?	+

**Figure 3. (Continued)**

van Geldorp 1994	?	?	?	?	?	?	+
Wallweiner 1998	?	?	?	?	?	?	+

**Allocation**

**Sequence generation**

Ten studies were rated as having unclear risk of bias. Study authors did not detail the randomly assigned component despite stating that these were randomised studies (Azziz 1993; Franklin 1995; Greenblatt 1993; Korell 1994; Li 1994; Nordic APSG 1995; Saravelos 1996; Sekiba 1992; van Geldorp 1994; Wallweiner 1998). Nine studies were deemed to have low risk of bias for sequence generation (Canis 2014; Diamond 1996; Haney 1995; Keckstein 1996; Mais 1995a; Mais 1995b; Myomectomy ASG 1995; Takeuchi 2005; Tinelli 2011).

**Concealment of allocation**

Eight studies were deemed to have low risk of selection bias (Canis 2014; Diamond 1996; Haney 1995; Keckstein 1996; Li 1994; Mais 1995a; Mais 1995b; Myomectomy ASG 1995). The remaining 11 studies were deemed to have unclear risk of selection bias. Although five of these studies used sealed envelopes, investigators did not detail the methods used to develop and monitor the allocation process with sealed envelopes (Azziz 1993; Franklin 1995; Nordic APSG 1995; Saravelos 1996; Sekiba 1992).

**Blinding**

**Blinding of participants and personnel (performance bias)**

Due to the nature of the intervention and the lack of comparable placebo agents, no study achieved blinding of the primary surgeon. However, by revealing the treatment allocation only after completing the initial surgical intervention, seven studies were deemed to have minimised performance bias (Azziz 1993; Canis 2014; Diamond 1996; Franklin 1995; Haney 1995; Keckstein 1996; Li 1994).

Twelve studies were rated to have unclear risk of performance bias (Greenblatt 1993; Korell 1994; Mais 1995a; Mais 1995b; Myomectomy ASG 1995; Nordic APSG 1995; Saravelos 1996; Sekiba 1992; Takeuchi 2005; Tinelli 2011; van Geldorp 1994; Wallweiner 1998), as study authors did not clearly state whether participants were blinded and/or whether treatment allocation was revealed before or during the initial surgery.

**Blinding of outcome assessment (detection bias)**

Nine studies clearly stated that assessors at SLL were blinded (Canis 2014; Diamond 1996; Greenblatt 1993; Li 1994; Mais 1995a; Mais 1995b; Saravelos 1996; Sekiba 1992; Tinelli 2011). Two of these studies recorded the SLL in video, and blinded independent assessors watched those videos to grade the severity of adhesions (Canis 2014; Diamond 1996). However, in Canis 2014, video recording was not performed in seven of the SLL patients, meaning that these patients were not assessed by a blinded independent surgeon, potentially increasing the risk of detection bias. Therefore, we included only the data from independently performed SLL from Canis 2014 in our final data analysis.

Eight studies did not clearly state that the surgeon performing the SLL was blinded to the initial intervention (Franklin 1995; Keckstein 1996; Korell 1994; Myomectomy ASG 1995; Nordic APSG 1995; Takeuchi 2005; van Geldorp 1994; Wallweiner 1998).

Two studies were deemed to have high risk of detection bias, as the surgeons at SLL were not blinded to the intervention group (Azziz 1993; Haney 1995).

Fourteen studies blinded surgeons to randomisation at second-look laparoscopy, three studies did not discuss blinding (Haney 1995; Myomectomy ASG 1995; van Geldorp 1994), and two studies did not use blinding (Azziz 1993; Takeuchi 2005).

**Incomplete outcome data**

Four studies were rated as high risk, 10 as unclear risk, and five as low risk.

**Dropouts**

Azziz 1993 reported a large number of dropouts. A total of 198 participants were randomly assigned, but 64 were excluded from analysis because of inadequate documentation in 23, surgical technique and evaluation inconsistent with the protocol in 36, concurrent therapy in conflict with the protocol in three, and participant refusal to undergo second-look laparoscopy in two (Wiseman 1999), demonstrating high risk of bias. Keckstein 1996 also reported a large number of dropouts, with 8 of 25 participants not returning for SLL. No reason was given for this. Canis 2014 reported a large number of dropouts as well, with 7 of 61 patients not undergoing second-look laparoscopy and 21 of 61 not returning for three-year follow-up.

Tinelli 2011 reported participants undergoing a second surgical procedure within six years of initial surgery: 546 of 694 participants underwent a second surgery. In contrast to other trials, a second-look laparoscopy at a specified time interval was not performed on all participants, leading to the exclusion of 148 participants from the results; this increases the risk of attrition bias.

**Withdrawals and intention-to-treat analysis**

Withdrawals were stated in eleven studies (Azziz 1993; Canis 2014; Diamond 1996; Greenblatt 1993; Haney 1995; Keckstein 1996; Li 1994; Myomectomy ASG 1995; Saravelos 1996; Takeuchi 2005; Tinelli 2011), and three studies did not state withdrawals (Franklin 1995; Nordic APSG 1995; Sekiba 1992); in five studies, no dropouts were reported (Mais 1995a; Mais 1995b; Takeuchi 2005; van Geldorp 1994; Wallweiner 1998). No studies with dropouts performed an ITT analysis. A total of six participants from all studies were reported to have been unable to undergo second-look laparoscopy because of pregnancy.

**Selective reporting**

Two studies were rated as high risk (Li 1994; Nordic APSG 1995), and the other 17 studies were rated as unclear risk. The Nordic study reported larger numbers of participants randomly assigned

in meeting abstracts before the study was published in a journal (Nordic APSG 1995). The explanation for this discrepancy was that some participants who did not meet inclusion criteria were recruited and were not included in the final analysis (personal communication, Wiseman 1999). In the United Kingdom, centres other than Sheffield were randomly assigning participants in a study of oxidised regenerated cellulose versus no treatment in the early 1990s (personal communication, A Watson), but the data have never been published (Li 1994). Attempts to identify these data by contacting investigators and the sponsoring company (Ethicon, Bridgewater, New Jersey, USA) have proved fruitless thus far. In van Geldorp 1994, another centre was recruiting participants (investigator: Trimbos-Kemper, The Netherlands), but these results have been reported only briefly in a review (Wiseman 1999). Data regarding the use of oxidised regenerated cellulose must be interpreted with caution because of the high risk of bias.

Additional information was sought from some study authors; at the time of this writing, six replies had been received (Azziz 1993; Franklin 1995; Keckstein 1996; Myomectomy ASG 1995; Saravelos 1996; van Geldorp 1994).

Haney 1995 reported statistically significant reductions in the adhesion score, but it is not clear whether these analyses took account of the within-participant design. It should be noted that the incidence of adhesions in the oxidised regenerated cellulose arm of the trial is greater than would be expected from the RCTs of oxidised regenerated cellulose versus no barrier agent. As it was not clear from the publication whether the surgeon was unblinded at the time of the second-look laparoscopy, this result should be treated with some caution.

### Other potential sources of bias

#### Statistical analysis

Of the 10 studies using a within-participant design and reporting adhesion formation, only three presented and analysed matched data appropriately (Azziz 1993; Saravelos 1996; Sekiba 1992). Appropriate data were extracted from the reports of two others (Franklin 1995; Haney 1995), which were incorrectly analysed in the original. See [Methods](#) section for a full description. One further study failed to present comparative data and was excluded from all analyses (Greenblatt 1993).

### Effects of interventions

See: [Summary of findings for the main comparison Analysis 1 - Oxidised regenerated cellulose vs no treatment at laparoscopy for adhesion prevention after gynaecological surgery](#); [Summary of findings 2 Analysis 2 - Oxidised regenerated cellulose vs no treatment at laparotomy for adhesion prevention after gynaecological surgery](#); [Summary of findings 3 Analysis 4 - Expanded polytetrafluoroethylene vs oxidised regenerated cellulose for adhesion prevention after gynaecological surgery](#); [Summary of findings 4 Analysis 7 - Collagen membrane with polyethylene glycol and glycerol vs Ringer's lactate](#)

No studies reported either of our primary outcomes (pelvic pain and live birth).

### 1. Oxidised regenerated cellulose versus no treatment at laparoscopy

([Analysis 1.1](#); [Summary of findings for the main comparison](#))

#### Primary outcomes

##### 1.1 Pelvic pain

This was not assessed by any study.

##### 1.2 Live birth rate

This was not assessed by any study.

#### Secondary outcomes

##### 1.3 Adhesion score

This was not assessed by any study.

##### 1.4 Number of participants with adhesions at SLL

Six trials reported this outcome. Three reported de novo adhesion formation (Mais 1995b; Saravelos 1996; Tinelli 2011), and three reported re-formation of adhesions following adhesiolysis (Keckstein 1996; Mais 1995a; Wallweiner 1998); Keckstein 1996 reported both de novo and re-formation adhesions and was therefore included with the other studies reporting re-formed adhesions.

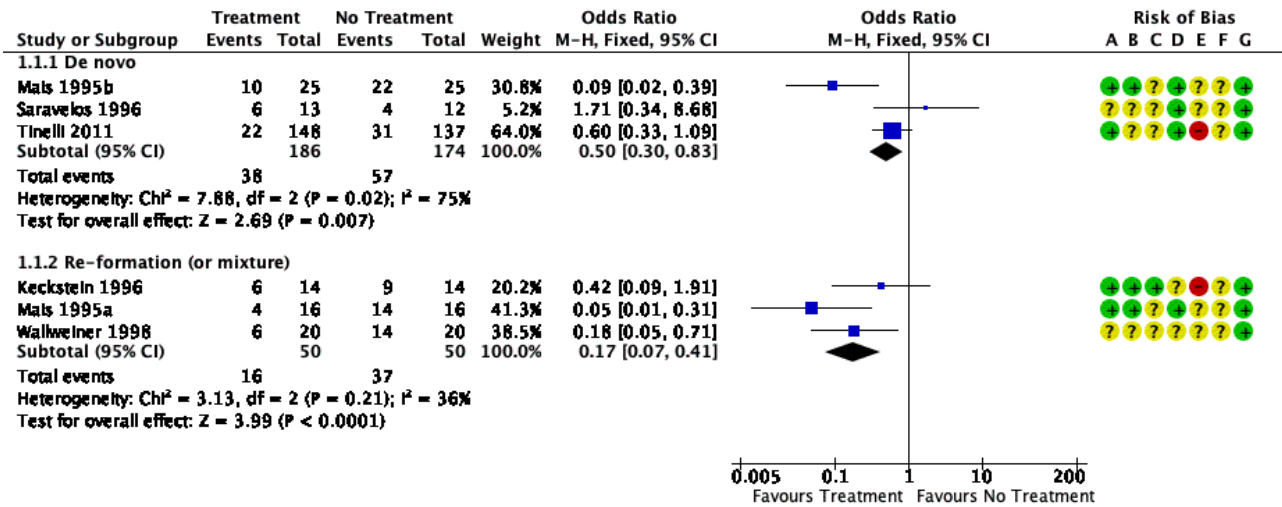
We are uncertain whether the use of oxidised regenerated cellulose reduced the incidence of de novo adhesions when compared with no treatment at second-look laparoscopy (OR 0.50, 95% CI 0.30 to 0.83, 3 trials, 360 participants;  $I^2 = 75%$ ; very low-quality evidence). This evidence would suggest that among women with a 48% chance of developing de novo adhesions with no treatment, the incidence of de novo adhesions using oxidised regenerated cellulose will be between 22% and 44%.

No clear explanation was provided for the high heterogeneity in this analysis ( $I^2 = 75%$ ). However, it is possible that the small number of participants within the included studies may partially account for it. Differences in operative procedure were observed between studies, as were differences in wrapping and use of oxidised regenerated cellulose (Saravelos 1996). It is unclear, however, whether these differences can account for the very high level of heterogeneity observed in these studies.

We are also uncertain whether the use of oxidised regenerated cellulose reduced the incidence of re-formed (or mixed) of adhesions (OR 0.17, 95% CI 0.07 to 0.41, 3 trials, 100 participants;  $I^2 = 36%$ ; very low-quality evidence). This evidence would suggest that among women with a 75% chance of developing re-formed (or mixed) adhesions with no treatment, the incidence of adhesion formation using oxidised regenerated cellulose will be between 18% and 55%.

See [Figure 4](#).

**Figure 4. Forest plot of comparison: 1 Oxidised regenerated cellulose (Interceed) vs no treatment at laparoscopy, outcome: 1.1 Incidence of adhesions.**



**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

**1.5 Clinical pregnancy rate**

This was not assessed by any study.

**1.6 Miscarriage rate**

This was not assessed by any study.

**1.7 Ectopic pregnancy rate**

This was not assessed by any study.

**1.8 Quality of life (QoL)**

This was not assessed by any study.

**1.9 Adverse outcomes**

Tinelli 2011 reported the incidence of fever within 48 hours as 6.5% to 12.5% of cases; this was likely to be secondary to surgery rather than to use of the barrier agent. Otherwise, no adverse outcomes were identified among the 236 participants receiving the intervention across studies (Keckstein 1996; Mais 1995a; Mais 1995b; Saravelos 1996; Tinelli 2011; Wallweiner 1998).

**2. Oxidised regenerated cellulose versus no treatment at laparotomy**

(Analysis 2.1; Summary of findings 2)

**Primary outcomes**

**2.1 Pelvic pain**

This was not assessed by any study.

**2.2 Live birth rate**

This was not assessed by any study.

**Secondary outcomes**

**2.3 Adhesion score**

This was not assessed by any study.

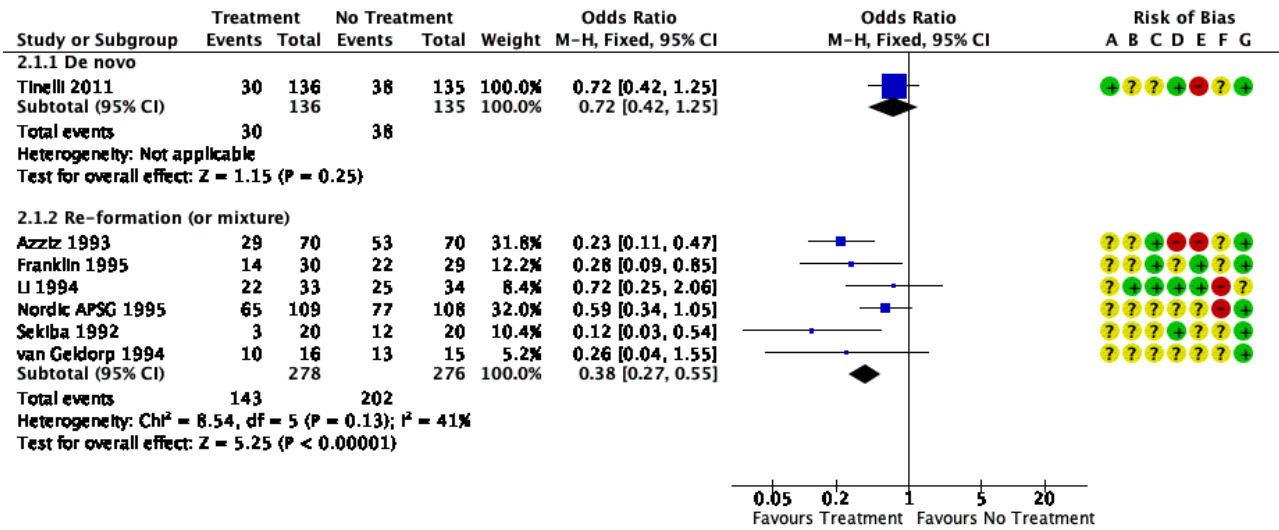
**2.4 Number of participants with adhesions at SLL**

Six trials reported on re-formation of adhesions following laparotomy for adhesiolysis - Azziz 1993, Li 1994, Nordic APSG 1995, Sekiba 1992 - and ovarian surgery - Franklin 1995, van Geldorp 1994. Use of oxidised regenerated cellulose may have resulted in a reduction in the incidence of re-formation adhesions compared with no treatment (OR 0.38, 95% CI 0.27 to 0.55, 6 trials, 554 participants; I<sup>2</sup> = 41%; low-quality evidence). This suggests that among women with a 75% chance of adhesion re-formation with no treatment, the incidence of adhesion re-formation using oxidised regenerated cellulose will be between 45% and 62%.

We are uncertain whether oxidised regenerated cellulose affected the formation of de novo adhesions following laparotomy (OR 0.72, 95% CI 0.42 to 1.25, 1 trial, 271 participants; very low-quality evidence). This suggests that among women with a 48% chance of developing de novo adhesions with no treatment, the incidence of de novo adhesions using oxidised regenerated cellulose will be between 28% and 54%.

See Figure 5.

**Figure 5. Forest plot of comparison: 2 Oxidised regenerated cellulose (Interceed) vs no treatment at laparotomy, outcome: 2.1 Incidence of adhesions.**



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

**2.5 Clinical pregnancy rate**

This was not assessed by any study.

**2.6 Miscarriage rate**

This was not assessed by any study.

**2.7 Ectopic pregnancy rate**

This was not assessed by any study.

**2.8 Quality of life (QoL)**

This was not assessed by any study.

**2.9 Adverse outcomes**

In [Azziz 1993](#), three adverse events occurred (atelectasis, postoperative ileus, fever and abdominal pain), and in [van Geldorp 1994](#), a decrease in haemoglobin was reported. These adverse effects are related to the surgery rather than to the barrier agent. Otherwise, no adverse outcomes related to the agent were identified among 225 participants receiving the intervention across five studies ([Azziz 1993](#); [Franklin 1995](#); [Nordic APSG 1995](#); [Tinelli 2011](#); [van Geldorp 1994](#)). Two studies did not report on adverse outcomes ([Li 1994](#); [Sekiba 1992](#)).

**3. Expanded polytetrafluoroethylene versus no treatment**

(Analysis 3.1)

**Primary outcomes**

**3.1 Pelvic pain**

This was not assessed by any study.

**3.2 Live birth rate**

This was not assessed by any study.

**Secondary outcomes**

**3.3 Adhesion score**

This was not assessed by any study.

**3.4 Number of participants with adhesions at SLL**

Only one trial reported this comparison and described a reduction in new adhesion formation among women undergoing myomectomy at laparotomy ([Myomectomy ASG 1995](#)). Use of expanded polytetrafluoroethylene may have resulted in a reduction in new adhesion formation (OR 0.17, 95% CI 0.03 to 0.94, 1 trial, 42 participants; low-quality evidence). This result was obtained by assuming the outcome least favourable to expanded polytetrafluoroethylene that was compatible with reported results.

**3.5 Clinical pregnancy rate**

This was not assessed by any study.

**3.6 Miscarriage rate**

This was not assessed by any study.

**3.7 Ectopic pregnancy rate**

This was not assessed by any study.

**3.8 Quality of life (QoL)**

This was not assessed by any study.



### 3.9 Adverse outcomes

No adverse outcomes were reported for 21 participants receiving the intervention in one trial ([Myomectomy ASG 1995](#)).

### 4. Expanded polytetrafluoroethylene versus oxidised regenerated cellulose

([Analysis 4.1](#) and [Analysis 4.2](#); [Summary of findings 3](#))

#### Primary outcomes

##### 4.1 Pelvic pain

This was not assessed by any study.

##### 4.2 Live birth rate

This was not assessed by any study.

#### Secondary outcomes

##### 4.3 Adhesion score

We are uncertain whether the use of expanded polytetrafluoroethylene affected the adhesion score at SLL when compared with oxidised regenerated cellulose (MD -3.79, 95% CI -5.12 to -2.46, 1 study, 62 participants; very low-quality evidence).

##### 4.4 Number of participants with adhesions at SLL

One trial reported no evidence of a difference in the formation of de novo adhesions following myomectomy at laparoscopy (OR 0.93, 95% CI 0.26 to 3.41, 1 trial, 38 participants; very low-quality evidence) ([Korell 1994](#)). This suggests that among women with a 15% chance of developing de novo adhesions with oxidised regenerated cellulose, the incidence of de novo adhesions using expanded polytetrafluoroethylene will be between 5% and 38%.

One trial reported this comparison for a reduction in re-formation of adhesions among women undergoing adhesiolysis at laparotomy ([Haney 1995](#)). We are uncertain whether the use of expanded polytetrafluoroethylene was associated with a reduction in adhesion re-formation (OR 0.13, 95% CI 0.02 to 0.80, 1 trial, 23 participants; very low-quality evidence). This suggests that among women with a 57% chance of adhesion re-formation with oxidised regenerated cellulose, the incidence of adhesion re-formation using expanded polytetrafluoroethylene will be between 3% and 52%. This finding was sensitive to choice of effect measure, just ceasing to show a reduction in adhesions when the risk of re-formed adhesions was analysed using risk ratio (RR 0.36, 95% CI 0.13 to 1.01).

##### 4.5 Clinical pregnancy rate

This was not assessed by any study.

##### 4.6 Miscarriage rate

This was not assessed by any study.

##### 4.7 Ectopic pregnancy rate

This was not assessed by any study.

##### 4.8 Quality of life (QoL)

This was not assessed by any study.

### 4.9 Adverse outcomes

Participants in [Haney 1995](#) experienced no adverse effects (three were treated with expanded polytetrafluoroethylene during surgery; nine were treated with oxidised regenerated cellulose). One study did not report whether adverse outcomes occurred ([Korell 1994](#)).

### 5. Sodium hyaluronate and carboxymethylcellulose versus no treatment

([Analysis 5.1](#))

#### Primary outcomes

##### 5.1 Pelvic pain

This was not assessed by any study.

##### 5.2 Live birth rate

This was not assessed by any study.

#### Secondary outcomes

##### 5.3 Adhesion score

[Diamond 1996](#) reported adhesion severity score with use of sodium hyaluronate with carboxymethylcellulose in comparison with no treatment, using a non-validated scoring method out of four. This showed that the use of sodium hyaluronate with carboxymethylcellulose probably resulted in a reduced adhesion severity score when compared with no treatment (MD 0.49, 95% CI 0.53 to 0.45, 1 trial, 127 participants; moderate-quality evidence; [Analysis 5.1](#)).

##### 5.4 Number of participants with adhesions at SLL

This was not assessed by any study.

##### 5.5 Clinical pregnancy rate

This was not assessed by any study.

##### 5.6 Miscarriage rate

This was not assessed by any study.

##### 5.7 Ectopic pregnancy rate

This was not assessed by any study.

##### 5.8 Quality of life (QoL)

This was not assessed by any study.

##### 5.9 Adverse outcomes

No adverse outcomes were reported in the 59 participants undergoing the intervention in one trial ([Diamond 1996](#)).

### 6. Fibrin sheet versus no treatment

([Analysis 6.1](#) and [Analysis 6.2](#))

#### Primary outcomes

##### 6.1 Pelvic pain

This was not assessed by any study.

##### 6.2 Live birth rate

This was not assessed by any study.

**Secondary outcomes**

**6.3 Adhesion score**

One study assessed fibrin sheet versus no treatment at laparoscopic myomectomy. Study authors reported no difference in adhesion grading, using a non-validated scoring method out of four (MD 0.14, 95% CI -0.67 to 0.39, 1 trial, 48 participants; very low-quality evidence).

**6.4 Number of participants with adhesions at SLL**

Only one study assessed fibrin sheet versus no treatment at laparoscopic myomectomy (Takeuchi 2005). Study authors reported the frequency and severity of postoperative adhesions. No evidence was found of differences between groups in the incidence of postoperative adhesions per participant (OR 1.20, 95% CI 0.42 to 3.41, 1 study, 62 participants; very low-quality evidence).

**6.5 Clinical pregnancy rate**

This was not assessed by any study.

**6.6 Miscarriage rate**

This was not assessed by any study.

**6.7 Ectopic pregnancy rate**

This was not assessed by any study.

**6.8 Quality of life (QoL)**

This was not assessed by any study.

**6.9 Adverse outcomes**

Participants in Takeuchi 2005 experienced no adverse effects (30 were treated with fibrin sheet during surgery).

**7. Collagen membrane with polyethylene glycol plus glycerol versus Ringer's lactate**

(Analysis 7.1, Analysis 7.2, Analysis 7.3, and Analysis 7.4; Summary of findings 4)

**Primary outcomes**

**7.1 Pelvic pain**

This was not assessed by any study.

**7.2 Live birth rate**

This was not assessed by any study.

**Secondary outcomes**

**7.3 Adhesion score**

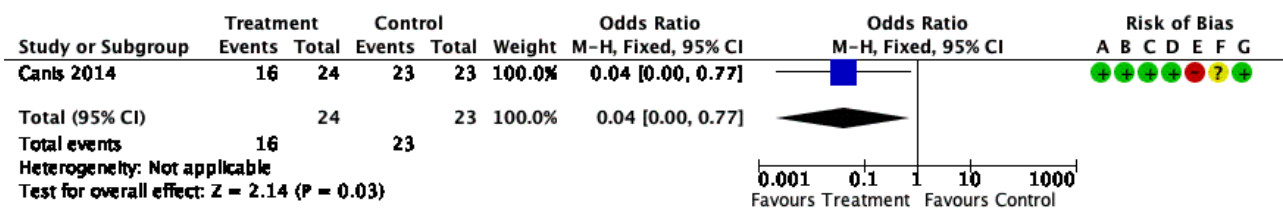
One study assessed collagen membrane with polyethylene glycol plus glycerol versus Ringer's lactate in myomectomy at laparotomy (Canis 2014). The study reports median rather than mean mAFS scores at SLL; however results appear to demonstrate no difference between groups (0.8 vs 1.2, 1 trial, 47 participants; very low-quality evidence).

**7.4 Number of participants with adhesions at SLL**

One study investigated the incidence of de novo adhesions with collagen membrane with polyethylene glycol plus glycerol versus Ringer's lactate in myomectomy at laparotomy (Canis 2014). This suggests that there may have been a lower incidence of adhesions at SLL in the collagen membrane with polyethylene glycol plus glycerol group when compared with the control group (OR 0.04, 95% CI 0.00 to 0.77, 1 trial, 47 participants; low-quality evidence) (Analysis 7.1). This suggests that among women with a 48% chance of developing de novo adhesions with no barrier, the incidence of de novo adhesions using collagen membrane with polyethylene glycerol plus glycol will be between 0% and 42%.

See Figure 6.

**Figure 6. Forest plot of comparison: 7 Collagen membrane with polyethylene glycol and glycerol vs Ringer's lactate, outcome: 7.1 Incidence of adhesions.**



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

**7.5 Clinical pregnancy rate**

One study assessed collagen membrane with polyethylene glycol and glycerol versus Ringer's lactate in myomectomy at laparotomy (Canis 2014). This suggests that collagen membrane

with polyethylene glycol and glycerol may have improved clinical pregnancy rate at three-year follow-up when compared with the control (OR 5.69, 95% CI 1.38 to 23.48, 1 trial, 39 participants; low-quality evidence; Analysis 7.3). This suggests that among women with a 23% chance of becoming clinically pregnant with no barrier,

the incidence of clinical pregnancy using collagen membrane with polyethylene glycol plus glycerol will be between 29% and 87%.

### 7.6 Miscarriage rate

This was not assessed by any study.

### 7.7 Ectopic pregnancy rate

One study assessed collagen membrane with polyethylene glycol plus glycerol versus Ringer's lactate in myomectomy at laparotomy (Canis 2014). At three-year follow-up of 39 participants, no ectopic pregnancies were reported in either study group (Analysis 7.4).

### 7.8 Quality of life (QoL)

This was not assessed by any study.

### 7.9 Adverse outcomes

Canis 2014 reported four participants in the collagen membrane with polyethylene glycol plus glycerol group who were hospitalised due to adverse events: one due to intra-abdominal bleeding, one with anaemia due to preoperative and postoperative bleeding, one with a parietal haematoma, and one with abdominal pain and digestive disorders.

### Other analyses

#### Sensitivity analyses

Three studies reported an unclear randomisation procedure (Greenblatt 1993; Haney 1995; Wallweiner 1998) (although additional information has been requested). Excluding these studies from the analyses did not substantially affect findings.

Azziz 1993 reported a large number of dropouts (64/198), but excluding this study from the analyses did not affect findings.

In other sensitivity analyses, use of a random-effects model, or of risk ratio rather than odds ratio, did not substantially change findings for any outcomes, except that in the comparison of expanded polytetrafluoroethylene versus oxidised regenerated cellulose (Analysis 4.2), the confidence interval crossed the line of no effect when a risk ratio rather than an odds ratio was calculated (RR 0.36, 95% CI 0.13 to 1.01).

#### Publication bias

Insufficient studies were included in any analysis to permit construction of a funnel plot, so we were unable to formally assess publication bias.

#### 'Summary of findings' tables

'Summary of findings' tables for Analyses 3, 5, and 6 have not been included in this update of the review but can be found in the last published version (Ahmad 2015).

## DISCUSSION

### Summary of main results

Review authors identified that no studies reported our primary outcomes of pelvic pain and live birth rate; therefore any conclusions discussed below relate solely to our secondary outcomes.

We found evidence that use of oxidised regenerated cellulose may reduce the incidence of re-formation of adhesions at laparotomy (low-quality evidence). We are uncertain whether use of oxidised regenerated cellulose reduces de novo adhesion formation or adhesion re-formation at laparoscopy. We are also uncertain whether the use of oxidised regenerated cellulose reduces de novo adhesion formation at laparotomy.

We are uncertain whether polytetrafluoroethylene reduces adhesion formation when compared with oxidised regenerated cellulose.

One study suggested that use of sodium hyaluronate with carboxymethylcellulose probably reduces adhesion formation after laparoscopy (moderate-quality evidence).

We are uncertain whether use of fibrin sheets reduces the formation of adhesions.

One study suggested that use of a collagen membrane with polyethylene glycol plus glycerol may reduce the formation of adhesions at laparotomy (low-quality evidence). Based on evidence from the same study, we are uncertain whether collagen membrane with polyethylene glycol and glycerol improved clinical pregnancy rate (low-quality evidence).

### Overall completeness and applicability of evidence

Most gynaecological surgery is associated with risk of pelvic adhesions. Clinical consequences of adhesions include pain, subfertility, and small-bowel obstruction, as well as complications of subsequent surgery. Minimally invasive techniques such as laparoscopy reduce the risk of de novo adhesion formation but do not eliminate it entirely. Studies included within this review therefore assessed both laparoscopy and laparotomy.

This review assessed the effectiveness of barrier agents in reducing adhesions following conservative gynaecological surgery. As noted above, pharmacological and fluid agents are assessed in a separate Cochrane Review.

Unfortunately, no studies in this review reported live birth rate or pelvic pain as a primary outcome but instead focused on extent of adhesion formation by incidence or by score. However, only six studies investigated the use of barrier agents in women seeking treatment to improve fertility. None of these studies reported adverse outcomes attributable to use of a barrier agent.

### Quality of the evidence

The included studies were at unclear risk of bias in most domains. The most common limitation was failure to report sufficient details of study methods. Studies were at high risk of bias related to attrition rates (four studies), selective reporting (two studies), and lack of blinding (one study). Reporting of adverse effects was inadequate. We were unable to formally assess the risk of publication bias. However, we note that 13 studies reported sponsorship, 12 of which were sponsored by companies that manufactured adhesion agents. Furthermore, evidence suggests that unpublished data may exist regarding oxidised regenerated cellulose. Specifically, centres in the United Kingdom were known to be randomly assigning participants for a study in 1990 (personal communication, AW), although only results from Sheffield were identified by our search (Li 1994). Evidence of duplicate publication



of data may contribute to increased risk of publication bias (Haney 1995).

Clinical heterogeneity between studies was observed, with differences in surgical technique and variable timing of second-look laparoscopy ranging from 23 days to 2.5 years. Considerable statistical heterogeneity was observed in the comparison of oxidised regenerated cellulose versus no treatment at laparoscopy ( $I^2 = 75\%$ ), for which no clear explanation was provided.

We graded the overall quality of the evidence using GRADE methods. The quality ranged from very low to moderate but was low or very low for most comparisons. The main limitations were imprecision and poor reporting of study methods. See [Summary of findings for the main comparison](#), [Summary of findings 2](#), [Summary of findings 3](#), and [Summary of findings 4](#).

Summary of findings tables for Analyses 3, 5, and 6 have not been included in this update and can be found in the last published version (Ahmad 2015).

### Potential biases in the review process

The review authors made every effort to identify all studies that should be considered for inclusion. However, it remains possible that some errors were made in the review process and some relevant publications may have been missed.

Since the time of the previous review, necessary details required for inclusion in Cochrane Reviews have increased substantially. Although all previously included studies were reassessed for bias, some information was required from the study authors themselves, and attempts were made to contact them.

Duplicate publication of data and existence of unreported data create a risk of bias. This is reflected in the GRADE rating of very low for oxidised regenerated cellulose versus no comparison at laparoscopy. This was often difficult to establish because the data were presented as abstracts at meetings (often by different study authors). For example, Haney 1995 had four abstract publications, and Keckstein 1996 had two abstract publications.

### Agreements and disagreements with other studies or reviews

A review published in 2010 concludes that the "evidence is not adequate for definite conclusions to be drawn, either in terms of efficacy or in terms of safety" with regard to anti-adhesion agents in gynaecological surgery (Pados 2010). This is consistent with the findings of this review, which has found very little evidence on clinically relevant endpoints. Furthermore, the generally low GRADE evidence quality ratings given to most of the outcomes in this review show how, on our assessment, considerable uncertainty remains regarding use of these agents for improving patient outcomes.

The guidelines of the Society of Obstetricians and Gynaecologists of Canada on use of adhesion agents in gynaecological surgery are consistent with the notion that evidence on the effects of barrier agents on long-term clinical outcomes such as chronic pelvic pain and infertility is insufficient (Robertson 2010). These guidelines also state, "Oxidized regenerated cellulose adhesion barrier is associated with reduced incidence of pelvic adhesion formation at both laparoscopy and laparotomy when complete haemostasis

is achieved." This information is somewhat consistent with that reported in this review, which found that oxidised regenerated cellulose may reduce the re-formation of adhesions at laparotomy. However, this review determined that the quality of evidence obtained ranged from very low to low; and due to poor quality of evidence we were uncertain of the benefits of oxidised regenerated cellulose at laparoscopy.

The guidelines of the Society of Obstetricians and Gynaecologists of Canada also state, "Polytetrafluoroethylene barrier is more effective than no barrier or oxidized regenerated cellulose in preventing adhesion formation" (Robertson 2010). This again is partially consistent with our conclusions, as we identified one study suggesting that use of expanded polytetrafluoroethylene may reduce formation of de novo adhesions at laparoscopy. However, we rated the quality of evidence as low. We also found one trial that suggested superiority of expanded polytetrafluoroethylene over oxidised regenerated cellulose for incidence of re-formation adhesions. We deemed this evidence to be of very low quality, as this was a very small, unblinded, privately funded study, and we are therefore uncertain whether polytetrafluoroethylene reduces adhesion formation when compared with oxidised regenerated cellulose.

Finally, Robertson 2010 states, "Chemically modified sodium hyaluronate/carboxymethylcellulose is effective in preventing adhesion formation, especially following myomectomies," although researchers warned that these results should be interpreted with caution on the basis of comments provided in the previous version of this review. Our updated review also agrees with this conclusion.

## AUTHORS' CONCLUSIONS

### Implications for practice

We found no evidence on the effects of barrier agents used during pelvic surgery on either pain or fertility outcomes in women of reproductive age, as no studies were identified that reported these outcomes.

Low-quality evidence suggests that oxidised regenerated cellulose, expanded polytetrafluoroethylene, sodium hyaluronate with carboxymethylcellulose, and collagen membrane with polyethylene glycol plus glycerol may all be more effective than no treatment in reducing the incidence of adhesion formation following pelvic surgery. We found no conclusive evidence on the relative effectiveness of these interventions. We are uncertain whether use of a fibrin sheet is more effective than no treatment. No adverse events directly attributed to the adhesion agents were reported. The quality of the evidence ranged from very low to moderate. The most common limitations were imprecision and poor reporting of study methods. Most studies were commercially funded, and publication bias could not be ruled out.

### Implications for research

Further high-quality studies with improved blinding of surgeons/outcome assessors, reduced selective reporting, and use of intention-to-treat analyses are required. Research should focus on the effects of barrier agents on clinical outcomes, with emphasis on fertility outcomes among women trying to conceive. Future studies should include women as the unit of randomisation, live birth and

pain as primary outcomes, and earlier second-look laparoscopy (within four to six weeks).

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Finally, we thank James Duffy, Cindy Farquhar, Andy Vail, Patrick Vanderkerchove, and David Wiseman for their contributions to the 2007 update to the review.

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Azziz 1993

Methods	Unit of randomisation: pelvic sidewall Method of randomisation: sealed envelopes, computer-generated Time of randomisation: at completion of surgery Blinding: second-look laparoscopy performed by the same surgeon
Participants	Patients undergoing pelvic adhesiolysis by laparotomy N = 134 (268 pelvic sidewalls)  Dropouts: 64 participants were excluded for surgical procedures and/or evaluations inconsistent with the protocol (39), for inadequate documentation (23), and for not returning for second-look laparoscopy (2) Some participants underwent additional surgical procedures (salpingostomy, myomectomy, tubal anastomosis, endometriosis treatment) Indication for surgery: infertility Pre-existing adhesions: yes Cause of adhesions: not stated (endometriosis included) Microsurgery: yes  Age, years: > 18 (not further specified)  Location: multi-centre trial at 13 centres in North America Timing and duration: 1986 to 1989
Interventions	Oxidised regenerated cellulose on pelvic sidewall vs uncovered opposite sidewall  Other adjuvants used: none
Outcomes	Adhesions at second-look laparoscopy: at 10 days to 14 weeks  1. Incidence <ol style="list-style-type: none"> <li>a. Per pelvic sidewall</li> <li>b. Per organ</li> <li>c. Matched pair analysis</li> <li>d. According to use of sutures</li> <li>e. According to presence of adhesions</li> </ol> 2. Extent: <ol style="list-style-type: none"> <li>a. Area</li> <li>b. Area differential</li> <li>c. % improvement</li> </ol> 3. Area: measured (not specified) 4. Severity (graded as filmy or severe) <ol style="list-style-type: none"> <li>a. According to type of initial adhesion</li> </ol> Adverse effects  No pregnancy outcomes
Notes	Trial supported by manufacturers of Interceed (Johnson & Johnson, Inc.) Additional information provided by first study author Documented with photographs and drawings Reports of an earlier trial with a smaller sample size were published in 1989 and 1990 (see references)

**Azziz 1993** (Continued)

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Assignment performed by computerised algorithm; however study authors state that this was performed by the study's sponsor, who manufactured the intervention of interest
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes were used for allocation; however no further details regarding the process of concealment are provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unit of randomisation was by ovary, so each participant received both intervention and control  Surgeon was not blinded, but treatment assignment was revealed only intra-operatively: "after completion of all operative procedures... a sealed envelope disclosed assignment of treated and untreated sidewall"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Surgeon who performed the initial laparotomy was also the surgeon who performed the second-look laparoscopy. As no independent observers were used, this could be a source of bias
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts: 64 participants were excluded for surgical procedures and/or evaluations inconsistent with the protocol (39), for inadequate documentation (23), and for not returning for second-look laparoscopy (2)
Selective reporting (reporting bias)	Unclear risk	Data presented as numbers of cases and percentages; no data conversion. P values stated for outcomes. No omission of outcomes and no subsets of data. However, no pre-published protocol for reference purposes
Other bias	Low risk	No other bias identified

**Canis 2014**

Methods	Unit of randomisation: women  Method of randomisation: random balanced table in numbered, sealed envelopes  Time of randomisation: following operation, before closure of abdominal cavity  Blinding: patients blinded, videotapes of surgery reviewed by independent blinded surgeons  Multi-centre trial
Participants	Patients undergoing myomectomy at laparotomy for excision of at least 1 myoma > 60 mm in diameter  N = 61  33 randomised to intervention (collagen membrane with polyethylene glycol and glycerol (PREVADH)) and 28 randomised to control (Ringer's lactate)  Dropouts: 2 patients from the intervention group withdrew due to subsequent operations; 5 patients (3 from the intervention group and 2 from the control group) did not undergo second-look laparoscopy. Videos of surgery in 7 patients (4 from the intervention group and 3 from the control group) were not assessed by independent blinded surgeons  Age, years: 20 to 42; median 34.0 in intervention group and 34.5 in control group

**Canis 2014** (Continued)

Exclusion criteria: endometriosis (stage > 1), preoperative embolisation, submucous myoma, chronic corticotherapy, immunosuppressive or immunomodulatory treatment, treatment with a gonadotrophin-releasing hormone (GnRH) analogue within 3 months of the study, adnexal adhesions discovered during surgery

Baseline characteristics: no significant differences between groups stated

Indication for surgery: preservation of fertility

Pre-existing adhesions: none

Microsurgery: no

Additional surgical procedures: none stated

Location: 11 centres in France

Timing: May 2006 to June 2008

Interventions	Collagen membrane with polyethylene glycol and glycerol (PREVADH) vs instillation of 500 mL Ringer's lactate  Other adjuvants used: none stated  Second-look laparoscopy: <ol style="list-style-type: none"> <li>1. Timing: 10 to 20 weeks following initial surgery</li> <li>2. Surgeon blinded: no</li> <li>3. Adhesiolysis: not stated</li> </ol>
Outcomes	Adhesions at second-look laparoscopy: <ol style="list-style-type: none"> <li>1. Adhesion score (AFS and mAFS)</li> <li>2. Adhesion incidence</li> <li>3. Incidence of severe adhesions</li> </ol> Pregnancy outcomes: <ol style="list-style-type: none"> <li>1. Clinical pregnancy rate</li> <li>2. Ectopic pregnancy rate</li> </ol> Adverse events
Notes	Study sponsored and funded by Covidien  Intention to treat  Surgery documented by video; however videos not analysed in 7 cases  Power calculation: stated 34 patients needed in each arm  Prospectively registered at US clinical trials database: NCT01388907

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation was performed using a balanced random numbers table
Allocation concealment (selection bias)	Low risk	Blinded, sealed, numbered envelopes were opened in the operating theatre to decide treatment allocation



**Canis 2014** (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study does not clearly state that patients were blinded, but most patients had the initial surgery and an SLL  Surgeons were not blinded, but the randomisation process was applied intra-operatively to reduce the risk of performance bias: "after the uterus was sutured, but before closing the abdominal wall, patients were randomly allocated to one of two treatment groups, application of the anti-adhesive film to the surgical site (P-Group), or instillation of 500 mL Ringer's lactate solution into the pelvic cavity (R-group, control)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent blinded surgeons were asked to review videos recorded during the second-look laparoscopy to assess for adhesion development
Incomplete outcome data (attrition bias) All outcomes	High risk	3-year assessments completed in only 61% of patients
Selective reporting (reporting bias)	Unclear risk	No clear omissions of outcomes; data presented clearly, no subsets of data omitted. No protocol identified for comparison.
Other bias	Low risk	Coeloscopy second-look adhesions performed later in control group than in intervention group (4.1 vs 2.9 months)  Recruitment stopped early despite initial sample size calculations requiring 80 patients  Interim analysis performed without type 1 error adjustment  Effectiveness of anti-adhesion film in preserving fertility interpreted with caution as confounding infertility factors unavailable and intention to preserve fertility may have changed during 3-year follow-up

**Diamond 1996**

Methods	Unit of randomisation: women Method of randomisation: computer-generated Timing of randomisation: end of surgery Blinding: surgeon unaware of randomisation at second-look laparoscopy Multi-centre trial
Participants	Women undergoing uterine myomectomy at laparotomy with at least 1 posterior uterine incision $\geq 1$ cm. Similar baseline characteristics, including age, size and number of myomas, and number of uterine incisions  N = 127 Microsurgery: no Dropouts: 6 (withdrew or excluded because of new medications) Age, years: 34 Location: USA (19 centres) Timing: 1993 to 1995 Pre-existing adhesions Cause of adhesions: not stated
Interventions	Sodium hyaluronate and carboxymethylcellulose vs no treatment
Outcomes	Adhesion formation at the time of second-look laparoscopy (mean days 23, range 7 to 70) Outcomes included number of adhesion sites, severity score, and surface area of uterine adhesions

**Barrier agents for adhesion prevention after gynaecological surgery (Review)**

**Diamond 1996** (Continued)

No pregnancy outcomes reported

Notes

Power calculations: not stated  
 Documented by video  
 Multi-centre trial  
 Sponsored by Genzyme  
 No intention-to-treat analysis

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Clear method of randomisation derived from computer-generated randomisation list</p> <p>No clear source of bias</p> <p>Quote: "at each centre each enrolled patient was assigned consecutively a study number that corresponded to an identically numbered sealed study envelope, which determined the patient's treatment assignment via a computer derived randomisation list. After completion of myomectomy, patients were randomised at each centre into two groups"</p>
Allocation concealment (selection bias)	Low risk	<p>Numbered, sealed envelopes created before patient enrolment used to provide allocation, decreasing risk of bias</p> <p>Quote: "at each centre each enrolled patient was assigned consecutively a study number that corresponded to an identically numbered sealed study envelope, which determined the patient's treatment assignment via a computer derived randomisation list. After completion of myomectomy, patients were randomised at each centre into two groups"</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Study authors do not explicitly state that patients were blinded, but all patients had the initial myomectomy and the SLL: "after completion of the myomectomy and associated procedures, but before closure of the abdominal cavity, patients were randomized at each center into two groups: no treatment controls and patients to receive the Seprafilm study device"</p> <p>Surgeons were not blinded, but randomisation took place intraoperatively to minimise performance bias: "after myomectomy, just before closure of the abdominal cavity, women randomized for no treatment (n = 68) received neither Seprafilm nor a placebo"</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Videotapes of the SLL were reviewed by an independent blinded observer: "videotapes recorded during laparoscopy subsequently were reviewed at a central site by a single independent observer blinded to the patient's treatment assignment, to serve as the basis for the efficacy data on Seprafilm"</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>6 (out of 127) participants were withdrawn</p>
Selective reporting (reporting bias)	Unclear risk	<p>Data presented graphically and as percentages. P values stated for outcomes. No omission of outcomes and no subsets of data. Although this was an infertility study, no pregnancy outcomes stated</p>
Other bias	Low risk	<p>No other bias identified</p>

## Franklin 1995

Methods	<p>Unit of randomisation: ovary Method of randomisation: blocks of 2 with sealed envelopes Timing of randomisation: during surgery Blinding: yes</p> <p>57 participants randomly assigned 2 exclusions 55 participants (110 ovaries) analysed</p> <p>Trial supported by manufacturers of Interceed (Johnson &amp; Johnson Medical, Inc.)</p>
Participants	<p>Patients undergoing bilateral ovarian surgery by laparotomy (N = 55) Dropouts: not stated Indication for surgery: bilateral ovarian disease (adhesions 37; tubal occlusion 7; PID history 4; endometriosis 5; other 2); not exclusively participants with infertility Pre-existing adhesions: some (39/55) Cause of adhesions: not stated (endometriosis included) Microsurgery at surgeon's discretion</p> <p>Age, mean, years: 29.9 (range 22 to 41)</p> <p>Location: 6 centres (Houston, Texas; Detroit, Michigan; Richmond, Virginia; Grand Rapids, Michigan - USA; Sydney - Australia; Danderyd - Sweden) Timing and duration: 1990 to 1993</p>
Interventions	<p>Oxidised regenerated cellulose on ovary vs uncovered opposite ovary</p> <p>Other adjuvants used: none</p> <p>Second-look laparoscopy</p> <ol style="list-style-type: none"> <li>1. Timing: 10 to 98 days after initial surgery</li> <li>2. Surgeon unaware: not stated</li> <li>3. Adhesiolysis: yes</li> </ol>
Outcomes	<p>Adhesions at second-look laparoscopy: second or third week</p> <ol style="list-style-type: none"> <li>1. Incidence:             <ol style="list-style-type: none"> <li>a. Per pelvic sidewall</li> <li>b. Matched pair analysis</li> <li>c. According to diagnosis</li> </ol> </li> <li>2. Extent:             <ol style="list-style-type: none"> <li>a. Area (measured with laparoscopic probe)</li> <li>b. Area differential</li> <li>c. % improvement</li> <li>d. According to diagnosis (area differential)</li> <li>e. According to time interval to SLL (area differential)</li> </ol> </li> <li>3. Severity:             <ol style="list-style-type: none"> <li>a. Graded 0 to 3 (0 = no adhesions; 1 = filmy adhesions; 2 = organised adhesions; 3 = cohesive adhesions)</li> <li>b. Grade differential</li> </ol> </li> </ol> <p>Pregnancy outcomes: nil Adverse effects</p>
Notes	<p>Power calculations: nil Preliminary report of this trial published as abstract in 1993 (see references) Documentation: video</p>

**Franklin 1995** (Continued)

Sponsored by Johnson & Johnson

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear description of method of randomisation provided  Quote: "before beginning the study, a treatment randomisation scheme was generated. Patients were randomised in blocks of two to provide balance with respect to the left and right ovaries"
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes used to conceal allocations; unclear but appear to have been created after randomisation already decided  Quote: "randomised treatment assignments were placed in sealed envelope for each patient, thereby blinding the surgeon to the treatment assignment during surgery"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unit of randomisation was by ovary, so each participant received both intervention and control  Surgeon was not blinded, but treatment assignment was revealed only intra-operatively: "randomized treatment assignments were placed in sealed envelopes for each patient, thereby blinding the surgeon to the treatment assignment during surgery. At that time, a sealed envelope was opened, disclosing the assignment of either the left or right ovary for wrapping with Interceed"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It is not stated whether the surgeon performing SLL was blinded to which ovary received which intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 exclusions (out of 57 participants): 1 due to complete lysis of adhesions, and the second due to severe adhesions of pelvic wall at SLL
Selective reporting (reporting bias)	Unclear risk	Data presented as numbers of cases; no data conversion. P values stated for outcomes. No omission of outcomes and no subsets of data. No pre-published protocol identified
Other bias	Low risk	No other bias identified

**Greenblatt 1993**

Methods	Unit of randomisation: ovary Method of randomisation: not stated Time of randomisation: at completion of surgery Blinding: surgeon at second-look laparoscopy unaware of side that was treated
Participants	Patients undergoing bilateral ovarian cautery by laparoscopy N = 8; 1 exclusion, 7 participants, 14 ovaries Indication for surgery: infertility due to clomiphene-resistant PCOS Pre-existing adhesions: no Microsurgery: no  Age, mean, years: 26.6 Duration of infertility, mean, years: 3.2 (range 1.5 to 5)

**Greenblatt 1993** (Continued)

Tubal status: normal HSG and laparoscopy  
Ovulatory status: BBT and serum progesterone  
Semen analysis: done but results not stated

Location: Canada  
Timing and duration: not stated

Interventions	Oxidised regenerated cellulose on ovary vs uncovered opposite ovary  Other adjuvants used: none  Second-look laparoscopy  1. Timing: 3 to 4 weeks after initial surgery 2. Surgeon unaware: yes 3. Adhesiolysis: yes
Outcomes	Adhesions at second-look laparoscopy: at 3 to 4 weeks  1. Incidence (per ovary) 2. Adhesion score 3. Scoring: revised AFS classification (Fertility and Sterility 1988;49:944-55)  Adverse effects Pregnancy outcomes stated but not by intervention, as unit of randomisation was ovaries
Notes	Power calculation: nil Documentation: video Sponsored by MRC Canada (Interceed provided by Johnson & Johnson) No intention-to-treat analysis

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement of method of random sequence generation. Quote: "Interceed was applied to one ovary, selected randomly"
Allocation concealment (selection bias)	Unclear risk	No clear statement of method of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unit of randomisation is ovary, so all women served as their own controls  Surgeon was not blinded to intervention. Study authors also do not state whether treatment allocation took place intraoperatively
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment was performed by an independent blinded surgeon: "three to 4 weeks later, subject returned to the surgical short-stay unit. They underwent a second laparoscopy performed by a different surgeon, unaware of which side had been wrapped with Interceed"
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 exclusion due to technical difficulty in applying oxidised regenerated cellulose
Selective reporting (reporting bias)	Unclear risk	Data presented as numbers of cases and percentages. P values stated for significant outcomes. No omission of outcomes and no subsets of data. No pre-published protocol identified

**Greenblatt 1993** (Continued)

Other bias	High risk	Study used within-participant design for reporting adhesion formation. However, study was unclear on presentation and analysis of matched data, and no comparative data were presented. As such, we were unable to extract appropriate data from the study
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**Haney 1995**

Methods	<p>Unit of randomisation: pelvic sidewall</p> <p>Method of randomisation: computerised randomisation table - sealed envelopes</p> <p>Timing of randomisation: at completion of surgery</p> <p>Blinding: not clear whether surgeon was aware of randomisation at second-look laparoscopy</p>
Participants	<p>Patients undergoing pelvic adhesiolysis and reconstructive pelvic surgery by laparotomy N = 29; 32 participants randomly assigned but 3 excluded (failed second-look laparoscopy) 29 participants (58 pelvic sidewalls) analysed</p> <p>Surgical procedures, in addition to adhesiolysis: salpingostomy, fimbrioplasty, ovarian cystectomy, endometriosis surgery</p> <p>Indication for surgery: not stated whether exclusively for infertility</p> <p>Pre-existing adhesions: yes</p> <p>Cause of adhesions: previous surgery 27; PID history 5 (endometriosis included)</p> <p>Microsurgery performed at surgeon's discretion</p> <p>Age, years, range: 18 to 40 (mean not stated)</p> <p>Location: USA (Durham, North Carolina; Atlanta, Georgia; Denver, Colorado; San Diego, California; Houston, Texas)</p> <p>Timing and duration: 1991 to 1993</p>
Interventions	<p>Expanded polytetrafluoroethylene on pelvic sidewall vs oxidised regenerated cellulose on opposite pelvic sidewall</p> <p>Other adjuvants used: antibiotics</p> <p>Second-look laparoscopy</p> <ol style="list-style-type: none"> <li>1. Timing: 1 to 6 weeks after initial surgery (mean 30 days)</li> <li>2. Surgeon unaware: not stated</li> <li>3. Adhesiolysis: yes</li> </ol>
Outcomes	<p>Adhesions at second-look laparoscopy</p> <ol style="list-style-type: none"> <li>1. Incidence</li> <li>2. Extent: area, area differential, % improvement</li> <li>3. Adhesion score</li> <li>4. Area: measured (not specified)</li> </ol> <p>Scoring (0 to 11) according to (1) extent: 0 = no adhesions; 1 = &lt; 25%; 2 = 25% to 50%; 3 = 50% to 75%; 4 = &gt; 75%; (2) type: 0 = none; 1 = filmy, transparent, avascular; 2 = opaque, transparent, avascular; 3 = opaque, capillaries present; 4 = opaque, large vessels; (3) tenacity: 0 = none; 1 = adhesions essentially fell apart; 2 = adhesions were lysed with traction; 3 = adhesions required sharp dissection</p> <p>Adverse effects</p> <p>Pregnancy outcomes: nil</p>
Notes	<p>Power calculations: nil</p> <p>Sponsorship: trial supported by manufacturers of Gore-Tex (Gore and Associates Inc., Flagstaff, Arizona, USA)</p>

**Haney 1995** (Continued)

Documentation of adhesions: no video or photographic records stated

Preliminary report of this trial published as abstract in 1992 and in 1994 (see references)

Potential duplicate publication of preliminary data in March 1993: further information requested

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Clear use of computerised randomisation: "randomization accomplished by RANDOM software; Digital Equipment Corporation, Manard, MA)"
Allocation concealment (selection bias)	Low risk	Sealed randomised envelopes concealed randomisation and were not opened until after patients had been intraoperatively deemed to be included in the study: "after adhesiolysis, the size of the resulting peritoneal defect was measured in square centimeters. At this point in the procedure, if the patient met the criteria for inclusion as a candidate for the study, a randomization envelope [...] was opened to reveal which sidewall was to be covered with PTFE and which was to be covered with oxidized cellulose"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unit of randomisation was either left or right pelvic sidewall, so every woman also served as her own control  Surgeon was not blinded, but treatment allocation took place intraoperatively: "after adhesiolysis, the size of the resulting peritoneal defect was measured in square centimeters. At this point in the procedure, if the patient met the criteria for inclusion as a candidate for the study, a randomization envelope [...] was opened to reveal which sidewall was to be covered with PTFE and which was to be covered with oxidized cellulose"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Surgeon performing the SLL was not blinded to which pelvic sidewall received which intervention. The PTFE barrier had to be sutured on the pelvic sidewall and needed to be removed in most cases during SLL, but the oxidised regenerated cellulose barrier was not sutured and had mostly dissolved at the time of SLL
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts: 32 participants randomly assigned but 3 excluded (failed second-look laparoscopy) 29 participants (58 pelvic sidewalls) analysed
Selective reporting (reporting bias)	Unclear risk	Data presented as scores and graphically presented. P values stated for outcomes. No omission of outcomes and no subsets of data. However, no pre-published protocol identified
Other bias	Low risk	No other bias identified

**Keckstein 1996**

Methods	Unit of randomisation: ovary Method of randomisation: toss of a coin Time of randomisation: at completion of surgery  Blinding: surgeon at second-look laparoscopy not aware of allocation
Participants	Patients undergoing bilateral ovarian cystectomy by laparoscopy  N = 25

**Keckstein 1996** (Continued)

14 participants with bilateral endometriomas, 6 with ovarian cysts and endometriosis, and 5 with ovarian cysts only

Dropouts: 8, not stated why

Some participants also underwent adhesiolysis and removal of endometriosis

Indication for surgery: ovarian cysts; not specifically participants with infertility

Pre-existing adhesions: some (but participants with dense adhesions excluded)

Cause of adhesions: not stated (endometriosis included)

Microsurgery: no

Timing not stated

Country: Germany (1 centre)

**Interventions**

Oxidised regenerated cellulose on ovary vs uncovered opposite ovary

Other adjuvants used: none

Suturing: 9 of 17 in the oxidised regenerated cellulose group; 3 of 17 in the non-oxidised regenerated cellulose group

Second-look laparoscopy

1. Timing: 8 to 30 weeks after initial surgery
2. Surgeon unaware: not stated
3. Adhesiolysis: not stated

**Outcomes**

Adhesions at second-look laparoscopy: 8 to 30 weeks

1. Incidence (per ovary) of de novo adhesions
2. Severity: graded as filmy, vascular, or dense
3. Area: estimated % of ovarian surface

Adverse effects

Pregnancy data nil

**Notes**

Power calculations: nil

Analysis sponsored by Johnson & Johnson only after study was completed

First presented as abstract in 1994

No photographic or video documentation

No intention-to-treat analysis

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Coin tosses were used as a simple method of randomisation  Quote: "the random assignment of one ovary for wrapping with Interceed was revealed to the surgeon after a coin toss"
Allocation concealment (selection bias)	Low risk	Coin toss took place intraoperatively
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unit of randomisation was each ovary, so all women acted as their own controls  Surgeon was not blinded, but treatment allocation took place intraoperatively: "at the end of cystectomy the random assignment of one ovary for wrapping with Interceed [...] was revealed to the surgeon after a coin toss"



**Keckstein 1996** (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study does not state whether the assessor during SLL was blinded to initial treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	8 dropouts (n = 25); no reasons stated as to why participants did not return for SLL
Selective reporting (reporting bias)	Unclear risk	Data presented as numbers of cases and percentages, as well as graphically. P values stated for significant outcomes. No omission of outcomes and no subsets of data. However, no pre-published protocol identified
Other bias	Low risk	No other bias identified

**Korell 1994**

Methods	Unit of randomisation: participant Method of randomisation: unknown Time of randomisation: unknown Blinding: unknown
Participants	Patients undergoing myomectomy by laparoscopy N = 38 Dropouts: not known Myomectomy details unknown  Indication for surgery: fibroids Pre-existing adhesions: no Microsurgery: no  Age, mean, SD: unknown  Location: Germany Timing and duration: unknown
Interventions	Oxidised regenerated cellulose applied to myomectomy incision(s) vs Gortex applied to myomectomy site(s)  Other adjuvants used: none  Second-look laparoscopy  1. Timing: unknown 2. Surgeon unaware: unknown 3. Adhesiolysis: unknown
Outcomes	Adhesions at second-look laparoscopy  1. Incidence (per participant) 2. Severity: graded as none, mild, and severe  Adverse effects: unknown  Pregnancy: unknown
Notes	Power calculations not stated Documentation not stated No source of funding stated

**Korell 1994** (Continued)

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated within study
Allocation concealment (selection bias)	Unclear risk	Not stated within study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated within study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated within study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of whether withdrawals or dropouts occurred during the study
Selective reporting (reporting bias)	Unclear risk	Data presented as numbers of cases and percentages. P values stated for significant outcomes. No omission of outcomes and no subsets of data. However, no pre-published protocol identified
Other bias	Low risk	No other bias identified

**Li 1994**

Methods	Unit of randomisation: pelvic sidewall Method of randomisation: computer-generated random numbers Time of randomisation: at completion of surgery Blinding: assessor unaware of which sidewall was treated  28 participants randomly assigned 1 exclusion (declined second-look laparoscopy) 27 participants (54 pelvic sidewalls) analysed  Trial supported by manufacturers of Interceed (Johnson & Johnson Medical, Ltd., UK)
Participants	Patients undergoing adhesiolysis by laparotomy (N = 28; 54 pelvic sidewalls, 1 withdrawal)  Indication for surgery: infertility 21; chronic pelvic pain 6 Pre-existing adhesions: yes Cause of adhesions: endometriosis 9; PID 10; previous surgery 5; uncertain 3 Microsurgery: yes  Age, years, mean: 30.4 (SD 4.5) No details on participants with infertility  Location: UK Timing and duration: 1989 to 1992
Interventions	Oxidised regenerated cellulose on pelvic sidewall vs uncovered opposite sidewall  (oxidised regenerated cellulose sutured in 3 cases)

**Barrier agents for adhesion prevention after gynaecological surgery (Review)**

**Li 1994** (Continued)

Other adjuvants used: intraperitoneal hydrocortisone in Intralipid

Second-look laparoscopy

1. Timing: 3 to 14 weeks after initial surgery
2. Surgeon unaware: yes
3. Adhesiolysis: not stated

**Outcomes**

Adhesions at second-look laparoscopy: 3 to 14 weeks after initial surgery

1. Incidence (per pelvic sidewall)
2. Extent: area, area differential, % improvement
3. Severity
4. Area: measured (not specified)

Adverse effects

Pregnancy outcomes: not stated

**Notes**

Documented with photographs and drawings at initial surgery and with video recording at second-look laparoscopy  
Sponsored by Johnson & Johnson  
Video at second-look laparoscopy  
No power calculations  
No intention-to-treat analysis

**Risk of bias**

<b>Bias</b>	<b>Authors' judgement</b>	<b>Support for judgement</b>
Random sequence generation (selection bias)	Unclear risk	Randomisation stated but no details of method provided  Quote: "the assignment of the test side for each woman was carried out before the study and was randomised blocks of two to provide balance"
Allocation concealment (selection bias)	Low risk	Allocation concealment using envelopes opened intraoperatively, reducing risk of bias  Quote: "a sealed envelope was then opened revealing which of the side walls was to receive Interceed"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unit of randomisation was either right or left side of pelvic wall, so every woman also acted as her own control  Surgeon was not blinded, but treatment allocation was revealed only intraoperatively
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent blinded surgeon performed assessments at second-look laparoscopy
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 exclusion (declined second-look laparoscopy)
Selective reporting (reporting bias)	High risk	Data presented as numbers of cases as well as graphically. P values stated for significant outcomes. No omission of outcomes and no subsets of data. Unclear whether power calculation performed

**Li 1994** (Continued)

Furthermore, despite 21 participants undergoing adhesiolysis for infertility, no pregnancy outcomes stated

It should also be noted that centres other than Sheffield - [Li 1994](#) - were randomly assigning participants around the UK for a study of oxidised regenerated cellulose and no treatment in the early 1990s (personal communication, A Watson). However, data have never been published

Other bias	Unclear risk	During surgery, "constant irrigation of the tissue with a physiological solution that contained heparin" was performed. Also, all patients received instillation of hydrocortisone in Intralipid
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**Mais 1995a**

Methods	<p>Unit of randomisation: participant  Method of randomisation: random numbers table - numbered sealed envelopes  Time of randomisation: at completion of surgery  Blinding: yes</p> <p>32 participants  No exclusions stated</p> <p>No source of funding stated</p>
Participants	<p>Patients undergoing pelvic adhesiolysis and endometriosis treatment by laparoscopy (N = 32)  Dropouts: nil</p> <p>Endometriosis treatment consisted of coagulation or resection of implants and endometriomas, followed by a 3-month course of GnRH agonist</p> <p>Indication for surgery: not stated; not specifically participants with infertility  Pre-existing adhesions: yes  Cause of adhesions: endometriosis (stage IV)  Microsurgery: no</p> <p>Age, years, mean (SD): treatment group 30.1 (6.5); controls 29.3 (6.2)</p> <p>Location: Italy  Timing and duration: January 1993 to June 1994</p>
Interventions	<p>Oxidised regenerated cellulose on ovaries and de-peritonealised areas vs surgery only</p> <p>Other adjuvants used: none</p> <p>Second-look laparoscopy</p> <ol style="list-style-type: none"> <li>1. Timing: 12 to 14 weeks after initial surgery</li> <li>2. Surgeon unaware: yes</li> <li>3. Adhesiolysis: not stated</li> </ol>
Outcomes	<p>Adhesions at second-look laparoscopy 12 to 14 weeks later</p> <ol style="list-style-type: none"> <li>1. Incidence (per participant)</li> </ol> <p>Adverse effects</p> <p>Pregnancy outcomes: nil</p>
Notes	<p>Power calculation done  Documentation: video</p>

**Mais 1995a** (Continued)

Sponsorship: not stated

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned (using numbered sealed envelopes) to undergo surgery alone or surgery with an oxidised regenerated cellulose barrier. Treatment or control assignment was obtained by using a table of random digits. The envelope seal was broken in the operation room after completion of all operative procedures and before removal of laparoscopic ports
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used to conceal allocation. The envelope seal was broken in the operation room after completion of all operative procedures and before removal of laparoscopic ports
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Does not state whether initial surgeon was blinded; however as control was no treatment, appears unlikely that they were. Not clearly stated whether participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent blinded surgeons performed second-look laparoscopy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of whether withdrawals or dropouts occurred during the study
Selective reporting (reporting bias)	Unclear risk	Data reported in incidences/percentages. No range or CI reported. P values reported only for significant results. No conversion of data or subsets
Other bias	Low risk	No other bias identified

**Mais 1995b**

Methods	Unit of randomisation: participant Method of randomisation: random numbers table - numbered sealed envelopes Time of randomisation: at completion of surgery Blinding: double
Participants	Patients undergoing myomectomy by laparoscopy N = 50 Dropouts: nil Myomectomy consisted of removal of 1 to 4 myomas; largest was 3 to 6 cm  Indication for surgery: fibroids; not specifically participants with infertility Pre-existing adhesions: no Microsurgery: no  Age, years, mean (SD): treatment group 34.1 (5.7); control group 33.2 (5.5)  Location: Italy Timing and duration: January 1993 to June 1994
Interventions	Oxidised regenerated cellulose on myomectomy incision(s) vs uncovered myomectomy site(s)  Other adjuvants used: none

**Barrier agents for adhesion prevention after gynaecological surgery (Review)**

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**Mais 1995b** (Continued)

- Second-look laparoscopy
1. Timing: 12 to 14 weeks after initial surgery
  2. Surgeon unaware: yes
  3. Adhesiolysis: not stated

Outcomes	Adhesions at second-look laparoscopy 12 to 14 weeks later <ol style="list-style-type: none"> <li>1. Incidence (per participant)</li> <li>2. Severity: graded as filmy and avascular, dense and/or vascular, or cohesive</li> </ol> Adverse effects  Pregnancy: not stated
Notes	Power calculations: nil Documentation: not stated No source of funding stated

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment or control assignment was obtained by using a table of random digits
Allocation concealment (selection bias)	Low risk	Numbered, sealed envelopes were used to conceal allocation. The envelope seal was broken in the operation room after completion of all operative procedures and before removal of laparoscopic ports
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Does not state whether initial surgeon was blinded; however as control was no treatment, appears unlikely that they were. Not clearly stated whether participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Independent blinded surgeons performed second-look laparoscopy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of whether withdrawals or dropouts occurred during the study
Selective reporting (reporting bias)	Unclear risk	Data reported in incidences/percentages. No range or CI reported. P values reported only for significant results. No conversion of data or subsets
Other bias	Low risk	No other bias identified

**Myomectomy ASG 1995**

Methods	Unit of randomisation: myomectomy site Method of randomisation: computerised randomisation table - sealed envelopes Timing of randomisation: at completion of surgery Blinding: not stated whether surgeon was aware of randomisation at second-look laparoscopy
Participants	Patients undergoing myomectomy (2 or more) by laparotomy N = 28

**Barrier agents for adhesion prevention after gynaecological surgery (Review)**

**Myomectomy ASG 1995** (Continued)

1 exclusion (declined second-look laparoscopy)  
27 participants (54 myomectomy sites) analysed  
All had 2 myomectomy incisions of similar length and > 2 cm apart located on the fundus and on the posterior uterine wall

Indication for surgery: fibroids; not exclusively participants with infertility  
Microsurgery: no  
Pre-existing adhesions: no

Age, years, range: 18 to 43

Location: USA (Durham, North Carolina; Houston, Texas; Atlanta, Georgia; San Diego, California) and Canada (Montreal)  
Timing and duration: 1991 to 1993

Interventions	<p>Expanded polytetrafluoroethylene over myomectomy site vs uncovered myomectomy site</p> <p>Other adjuvants used: antibiotics</p> <p>Second-look laparoscopy</p> <ol style="list-style-type: none"> <li>1. Timing: 2 to 6 weeks after initial surgery (mean 25 days)</li> <li>2. Surgeon unaware: not stated</li> <li>3. Adhesiolysis: yes</li> </ol>
Outcomes	<p>Adhesions at second-look laparoscopy: 2 to 6 weeks after initial surgery</p> <ol style="list-style-type: none"> <li>1. Incidence (per myomectomy site)</li> <li>2. Extent: area</li> <li>3. Adhesion score</li> <li>4. Area: measured (not specified)</li> </ol> <p>Scoring (0 to 11) according to (1) extent: 0 = no adhesions; 1 = &lt; 25%; 2 = 25% to 50%; 3 = 50% to 75%; 4 = &gt; 75%; (2) type: 0 = none; 1 = filmy, transparent, avascular; 2 = opaque, transparent, avascular; 3 = opaque, capillaries present; 4 = opaque, large vessels; (3) tenacity: 0 = none; 1 = adhesions essentially fell apart; 2 = adhesions were lysed with traction; 3 = adhesions required sharp dissection</p> <p>Adverse effects</p> <p>Pregnancy outcomes: nil</p>
Notes	<p>Documented with diagrams, photographs, and videotapes</p> <p>Sponsored by Gore-Tex Surgical Membrane</p> <p>Multi-centre trial</p> <p>Power calculations: nil</p> <p>Preliminary reports of this trial published as abstracts 1993 and 1994</p> <p>No intention-to-treat analysis</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed using a computerised randomisation table
Allocation concealment (selection bias)	Low risk	Assignments were concealed in sealed envelopes opened intraoperatively
Blinding of participants and personnel (performance bias)	Unclear risk	No clear statement whether initial surgeon or participants were blinded



**Myomectomy ASG 1995** (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement whether surgeon performing second-look laparoscopy or assessment at SLL was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant withdrew from study before SLL
Selective reporting (reporting bias)	Unclear risk	Data presented as incidence of adhesions with CI and adhesion scores as means $\pm$ SEM. P values reported. No omissions or subsets of data. However, no pre-published protocol identified
Other bias	Low risk	No other bias identified

**Nordic APSG 1995**

Methods	Unit of randomisation: adnexae Method of randomisation: sealed envelopes Timing of randomisation: at completion of surgery Blinding: yes  66 participants (132 ovaries) No exclusions stated  Trial supported by manufacturers of Interceed (Johnson & Johnson, Stockholm, Sweden)
Participants	Patients undergoing adhesiolysis by laparotomy N = 66 (14 more were erroneously entered, as they did not meet entry criterion of pre-existing adhesions) Indication for surgery: infertility Pre-existing adhesions: yes Cause of adhesions: not stated (endometriosis excluded) Microsurgery: yes  Age: not stated No details on infertility status (duration of infertility, tubal status, ovulatory status, semen analysis)  Location: Scandinavia, Sweden (Stockholm, Linkoping, Goteborg, Gavle, Umea, and Skovde); 1 in Finland (Oulo), 1 in Denmark (Aalborg) Timing and duration: 1991 to 1993
Interventions	Oxidised regenerated cellulose on ovary and fallopian tube vs uncovered opposite side  Other adjuvants used: none  Second-look laparoscopy  1. Timing: 4 to 10 weeks after initial surgery 2. Surgeon unaware: not stated 3. Adhesiolysis: not stated
Outcomes	Outcomes analysed in review  Adhesions at second-look laparoscopy

**Nordic APSG 1995** (Continued)

1. Incidence:
  - a. Per ovary
  - b. Per tube
  - c. Per fimbria
2. Adhesion score (0-4) (max score = 24; 0 = no adhesions; 1 = minimal adhesions; 2 = mild adhesions: 1 or 2 simple thin strands less than 1 cm in width; 3 = moderate adhesions: more than 2 adhesions of type 2 or at least 1 solid adhesion; 4 = severe adhesion: more than type 3):
  - a. In aggregate
  - b. Per ovary
  - c. Per tube
  - d. Per fimbria

Adverse effects

Pregnancy outcomes: nil

Notes	Power calculations: nil Sponsored by Johnson & Johnson Multi-centre trial Duplicate publication with Larsson 93 (but different numbers)  Preliminary reports of this trial published as abstracts in 1993 and 1994 (see references)
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**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement regarding method of randomisation
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes used for allocation concealment but unclear when sealed or opened. Quote: "a sealed envelope disclosed assignment of which side was to be treated with the adjuvant therapy"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unit of randomisation was right or left adnexa, so every woman also acted as her own control  Not clearly stated whether surgeon was blinded, or when treatment allocation was revealed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement whether surgeon performing second-look laparoscopy or assessment at SLL was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of whether withdrawals or dropouts occurred during the study
Selective reporting (reporting bias)	High risk	Data presented in graphical form, as well as in tables as means $\pm$ SEMs. P values reported in table. Data reported for adhesions on ovaries, fallopian tubes, fimbriae. Data reported elsewhere with different sample size. Despite being an infertility study, pregnancy outcomes not stated
Other bias	Low risk	No other bias identified

## Saravelos 1996

Methods	Unit of randomisation: ovaries Method of randomisation: computer-generated in opaque envelopes Timing of randomisation: unclear Blinding: double
Participants	Women (N = 21) undergoing treatment for polycystic ovarian syndrome by ovarian electrocautery 7 dropouts: 4 were pregnant, 2 withdrew, 1 had such dense adhesions at laparoscopy of both ovaries that no assessment could be made  Pre-existing adhesions: nil Mean age, years: 28 No other cause for infertility found Timing: 1994 to 1995  Country: UK (1 centre)
Interventions	Oxidised regenerated cellulose vs no treatment
Outcomes	Adhesion formation  1. Incidence 2. Extent 3. Severity  Further adhesiolysis Timing of second-look laparoscopy: 2 to 11 weeks Pregnancy: outcomes given but ovaries randomly assigned, not participants
Notes	Supported by Johnson & Johnson Video taken Power calculations: nil No intention-to-treat analysis

### Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement provided regarding method of randomisation
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes used for allocation concealment but unclear when sealed or opened. Quote: "a sealed envelope disclosed the assignment of which side was to be treated with Interceed"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unit of randomisation was right or left ovary, so every woman also acted as her own control  Not clearly stated whether surgeon was blinded, or when treatment allocation was revealed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Second-look laparoscopy was video-recorded and assessed by independent blinded assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 participant excluded, as underwent ovarian drilling; 4 withdrew because of pregnancy; 2 withdrew because of personal choice (n = 21)

**Saravelos 1996** (Continued)

Selective reporting (re-reporting bias)	Unclear risk	Data reported as incidences and percentages. No data conversion. No P values reported
Other bias	Low risk	No other bias identified

**Sekiba 1992**

Methods	<p>Unit of randomisation: pelvic sidewall Method of randomisation: sealed envelopes Time of randomisation: at completion of surgery Blinding: double</p> <p>63 participants (126 pelvic sidewalls) No exclusions stated</p> <p>Trial supported by manufacturers of Interceed (Johnson &amp; Johnson Medical, KK, Tokyo, Japan)</p>
Participants	<p>Participants undergoing adhesiolysis by laparotomy N = 63</p> <p>Dropouts: not stated Indication for surgery: infertility, known presence of bilateral sidewall adhesions Pre-existing adhesions: yes Cause of adhesions: severe endometriosis 28; previous surgery 15; PID 9; no obvious cause 19 Microsurgery: no</p> <p>Country: Japan Timing and duration: not stated</p>
Interventions	<p>Oxidised regenerated cellulose on pelvic sidewall vs uncovered opposite sidewall</p> <p>Other adjuvants used: none</p> <p>Second-look laparoscopy</p> <ol style="list-style-type: none"> <li>1. Timing: 10 days to 14 weeks after initial surgery</li> <li>2. Surgeon unaware: yes</li> <li>3. Adhesiolysis: not stated</li> </ol>
Outcomes	<p>Adhesions at second-look laparoscopy at 10 days to 14 weeks</p> <ol style="list-style-type: none"> <li>1. Incidence (per pelvic sidewall)</li> <li>2. Extent: area, area differential, % improvement</li> <li>3. Area: measured with sterile ruler</li> <li>4. Incidence according to size of de-peritonealised area</li> <li>5. Incidence according to presence or absence of endometriosis</li> <li>6. Incidence according to use of sutures</li> <li>7. Extent (% improvement) according to size of de-peritonealised area</li> <li>8. Extent (% improvement) according to presence or absence of endometriosis</li> <li>9. Extent (% improvement) according to use of sutures</li> </ol> <p>Pregnancy outcomes: nil</p>
Notes	<p>Documented with photographs and drawings No power calculations Duplicate publication Supported by Johnson &amp; Johnson</p>

**Sekiba 1992** (Continued)

Multi-centre trial

Trial also published elsewhere in 1993 (see references)

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement provided regarding method of randomisation
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes used for allocation concealment but unclear when sealed or opened. Quote: "the pelvic sidewall to be covered was determined randomly using sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unit of randomisation was right or left pelvic sidewall, so every woman also acted as her own control  Not clearly stated whether surgeon was blinded, or when treatment allocation was revealed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessor performing second-look laparoscopy was blinded to allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of whether withdrawals or dropouts occurred during the study
Selective reporting (reporting bias)	Unclear risk	Data presented in graphical form for some outcomes. P values stated for significant outcomes. No data subsets reported. No pregnancy outcomes reported despite being an infertility study
Other bias	Low risk	No other bias identified

**Takeuchi 2005**

Methods	Unit of randomisation: participant Method of randomisation: computer-generated Time of randomisation: before surgery Blinding: absent
Participants	Women (N = 146) undergoing laparoscopic myomectomy; 69 in control group, 68 in fibrin gel group, and 68 in fibrin sheet group 2 became pregnant, 23 had other surgical procedures, 29 women with fibroid < 5 cm were excluded Pre-existing adhesions: nil Mean age: no statistically significant difference Timing: 2001 to 2002 Country: multi-centric
Interventions	Fibrin sheet placed on site of myomectomy wound vs uncovered wound  Other adjuvants used: none  Second-look laparoscopy  1. Timing: between 13 and 19 weeks after initial surgery 2. Surgeon unaware: yes

**Takeuchi 2005** (Continued)

3. Adhesiolysis: in participants who had adhesions present at second-look laparoscopy

Outcomes	Adhesions at second-look laparoscopy at 13 to 16 weeks 1. Incidence (adhesion formation per participant) 2. Adverse effects
Notes	Documentation of adhesions unclear No power calculations Support funding: unclear Multi-centre trial

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed using computer-generated lists
Allocation concealment (selection bias)	Unclear risk	Not clearly stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clearly stated whether participants or initial surgeons were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly stated whether surgeon performing or assessing second-look laparoscopy was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	High attrition rate, with only 91 of 146 patients undergoing SLL  Quote: "SLL was planned for 146 patients," "23 patients who underwent other surgical procedures (prior to SLL) were excluded," "29 patients in whom the maximum myoma diameter was < 5 cm were excluded," "[for] 2 women SLL was cancelled because they became pregnant," "consequently, 91 patients who underwent (surgery) alone were evaluated"
Selective reporting (reporting bias)	Unclear risk	Data reported as incidences and percentages. P values reported only for significant outcomes. No subsets of data. No pre-published protocol identified. mAFS score done, but no standard deviations reported (review authors unable to extract standard deviations from data published in study paper because of the way they had been presented)
Other bias	Low risk	No other bias identified

**Tinelli 2011**

Methods	Unit of randomisation: 546 participants Time of randomisation: at completion of surgery Blinding: single  Method of randomisation: block randomisation was used to ensure balance in the numbers of participants in the 4 treatment arms. A statistician generated the entire randomisation sequence list in advance, and allocations were sequentially numbered from beginning to end
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**Tinelli 2011** (Continued)

Exclusion criteria for the investigation: previous uterine or pelvic surgery; previous abdominal general surgery; presurgical treatment with GnRH analogues; gynaecological malignancy; pregnancy; use of any instillation such as 32% dextran-70, corticosteroids, anticoagulants, or non-steroidal anti-inflammatory drugs; haematological or coagulation disorders; presence of ongoing pelvic infection

Participants	<p>546 participants underwent surgery</p> <p>Type of surgery: laparoscopic or abdominal single or multiple intracapsular myomectomy</p> <p>Reasons for surgery: pelvic pain, menorrhagia and growth of fibroids as verified by ultrasound; some women requested myomectomy because of infertility</p> <p>Mean age between groups, years: 28.9 to 30.2</p> <p>Timing of second-look surgery between groups, years: 2.3 to 2.6</p> <p>Dates: January 2003 to June 2009</p>
Interventions	<p>Participants were subdivided into groups for laparoscopic or abdominal surgery. Participants underwent single or multiple intracapsular myomectomy. Participants were randomly assigned to placement of oxidised regenerated cellulose absorbable adhesion barrier to the uterine incision or to control without barriers</p>
Outcomes	<p>Primary and secondary outcomes of analysis: presence and severity of adhesions for 4 groups: laparotomy with barrier, laparotomy without barrier, laparoscopy with barrier, and laparoscopy without barrier</p>
Notes	<p>Funding: no external source stated</p> <p>Power calculation: stated</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Randomisation list used to reduce bias</p> <p>Quote: "after completion of reconstructive uterine surgery, subjects were assigned to the treatment in a 1:1 ratio using a randomization list with random permuted blocks, length of 4"</p>
Allocation concealment (selection bias)	Unclear risk	<p>Methods of allocation concealment not stated in the text</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>Not stated whether initial surgeon was blinded; however as control was no treatment, this appears unlikely. Not clearly stated whether participants were blinded</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Surgeons who performed second-look laparoscopy and assessment were blinded to treatment allocation</p>
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>High attrition rate, intentionally excluding patients not requiring repeat surgery, even though these patients may have had asymptomatic adhesions</p> <p>Quote: "of the 694 enrolled patients, 546 (78%) were available for assessment of adhesions during a subsequent operation"</p> <p>Adhesions were assessed at second surgery only if the participant had undergone subsequent surgery over the 6 years. Arguably, study data may be</p>



**Tinelli 2011** (Continued)

skewed by not including the 21% of participants who did not require subsequent surgery. Reasons for subsequent surgery include "laparotomy for cesarean section, laparotomy or laparoscopy for ovarian cysts, recurrent fibroids, appendectomy, cholecystectomy, extrauterine pregnancy and infertility"

Selective reporting (reporting bias)	Unclear risk	Data reported as incidences and percentages. P values reported only for significant outcomes. No differences identified between methods and reported results. However, no pre-publication protocol identified for reference purposes
Other bias	Low risk	No other bias identified

**van Geldorp 1994**

Methods	Unit of randomisation: ovary Method of randomisation: computer-generated by telephone Time of randomisation: at completion of surgery Blinding: not stated
Participants	Patients undergoing bilateral ovarian surgery by laparotomy N = 20 participants (40 ovaries) No dropouts  Surgery consisted of adhesiolysis, ovarian cystectomy, and removal of endometriosis  Indication for surgery: not stated; not specifically participants with infertility Pre-existing adhesions: yes Cause of adhesions: endometriosis 14; others not stated Microsurgery: no  Age, years, mean: 31 (range 22 to 38)  Location: University Hospital, Rotterdam, The Netherlands Timing and duration: not stated
Interventions	Oxidised regenerated cellulose on ovary vs uncovered opposite ovary  Other adjuvants used: not stated  Second-look laparoscopy  1. Timing: 4 to 8 weeks after initial surgery 2. Surgeon unaware: not stated 3. Adhesiolysis: not stated
Outcomes	Adhesions at second-look laparoscopy  1. Incidence: a. Per ovary b. In aggregate c. In participants with endometriomas 2. Severity: a. In aggregate b. In participants with endometriomas 3. Area: measured (not specified) 4. Severity: graded as filmy, vascular, or dense

**van Geldorp 1994** (Continued)

5. Extent:
  - a. Area
  - b. Area differential
  - c. % improvement

Notes  
 Trial supported by Johnson & Johnson  
 Documentation: not stated  
 Power calculations: not stated

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	At the end of the procedure and after haemostasis was achieved, 1 ovary was chosen on a random basis
Allocation concealment (selection bias)	Unclear risk	At the end of the procedure and after haemostasis was achieved, 1 ovary was chosen on a random basis
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unit of randomisation was right or left ovary, so every woman also acted as her own control  Not clearly stated whether surgeon was blinded, or when treatment allocation was revealed
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly stated whether surgeon performing or assessing second-look laparoscopy was blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of whether withdrawals or dropouts occurred during the study
Selective reporting (reporting bias)	Unclear risk	Data reported as mean area $\pm$ SEM. P values reported for significant outcomes. No subsets of data. No pre-publication protocol for reference purposes
Other bias	Low risk	No other bias identified

**Wallweiner 1998**

Methods  
 Unit of randomisation: participant  
 Method of randomisation: not stated  
 Time of randomisation: at completion of surgery  
 Blinding: yes

Participants  
 Women (N = 40) undergoing initial treatment for endometriosis by laparoscopy-vaporisation of peritoneal deposits, excision of endometrioma, reconstructive surgery, and adhesiolysis  
 No dropouts  
  
 Mean age, years: 27  
 Pre-existing adhesions: yes  
 Cause of adhesions: endometriosis  
 Microsurgery: no  
 Location: Germany  
 Timing: not stated

**Wallweiner 1998** (Continued)

7 dropouts: 4 were pregnant, 2 withdrew, and 1 had such dense adhesions at laparoscopy of both ovaries that no assessment could be made

Pre-existing adhesions: nil

Mean age, years: 28

No other cause of infertility found

Timing: 1994 to 1995

Country: UK (1 centre)

Interventions	<p>Oxidised regenerated cellulose applied to all injured visceral peritoneal surfaces of ovary, tubes and uterus vs no treatment</p> <p>Other adjuvants used: none</p> <p>Second-look laparoscopy</p> <ol style="list-style-type: none"> <li>1. Timing: 3 to 6 months after initial surgery</li> <li>2. Surgeon unaware: yes</li> <li>3. Adhesiolysis: nil</li> </ol>
Outcomes	<p>Adhesions at second-look laparoscopy: 3 to 6 months later</p> <ol style="list-style-type: none"> <li>1. Incidence (per participant)</li> <li>2. Severity according to scoring system</li> <li>3. Surface area</li> <li>4. Extent: area, area differential, % improvement</li> <li>5. Incidence in participants with endometriomas</li> <li>6. Severity in participants with endometriomas</li> </ol> <p>Adverse outcomes: unknown</p> <p>Pregnancy: not stated</p>
Notes	<p>Power calculations: nil</p> <p>Sponsorship: not stated</p> <p>Documentation: video</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not clearly stated
Allocation concealment (selection bias)	Unclear risk	Not clearly stated in text
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated whether initial surgeon was blinded; however as control was no treatment, this appears unlikely. Not clearly stated whether participants were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States that evaluator performing second-look laparoscopy was not familiar with the initial operative site, but does not clearly state that evaluator was blinded to treatment allocation
Incomplete outcome data (attrition bias)	Unclear risk	No mention of whether withdrawals or dropouts occurred during the study

**Wallweiner 1998** (Continued)

All outcomes

Selective reporting (reporting bias)	Unclear risk	Data reported as numbers in a dichotomous score. P values stated. No conversion or subsets of data. No pre-publication protocol for reference purposes
Other bias	Low risk	No other bias identified

AFS: American Fertility Society.

BBT: basal body temperature.

CI: confidence interval.

GnRH: gonadotrophin-releasing hormone.

HSG: hysterosalpingogram.

mAFS: modified American Fertility Society.

PID: pelvic inflammatory disease.

PTFE: polytetrafluoroethylene.

SD: standard deviation.

SEM: standard error of the mean.

SLL: second-look laparoscopy.

**Characteristics of excluded studies** [ordered by study ID]

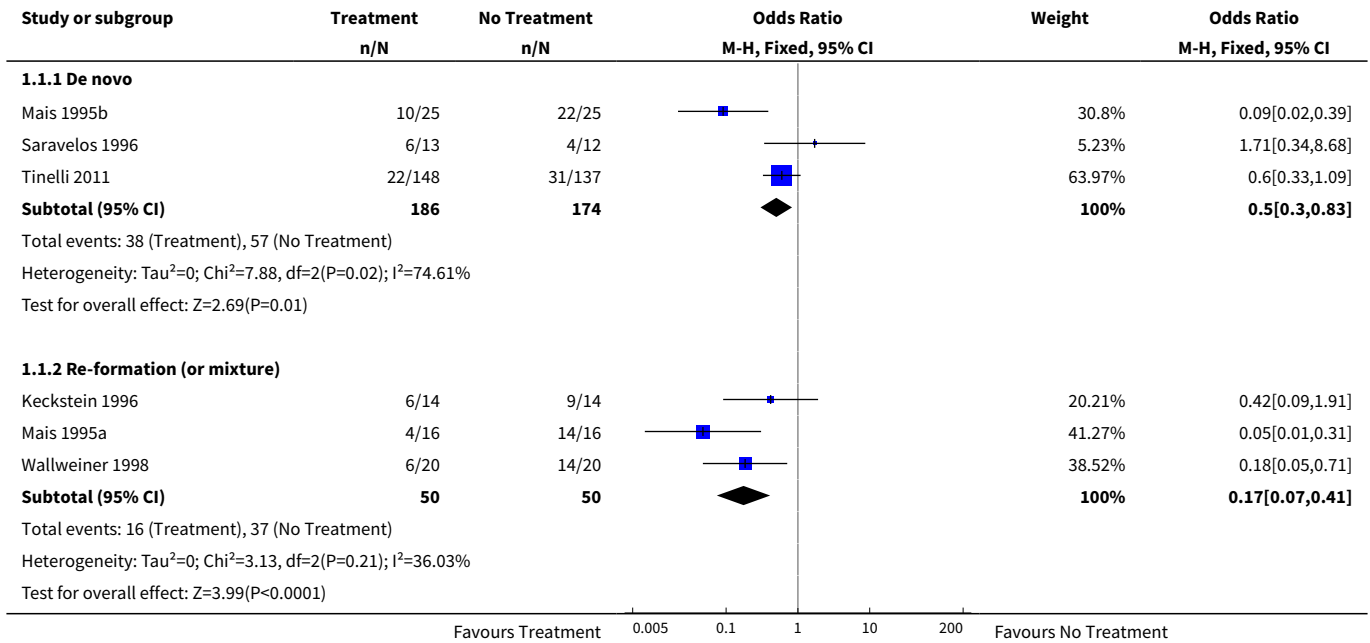
Study	Reason for exclusion
<a href="#">Diamond 1998</a>	Excluded, as trial intervention was a solution - not a barrier
<a href="#">Dunn 2002</a>	Excluded, as trial intervention was a solution - not a barrier
<a href="#">Korrell 1998</a>	Excluded, as trial intervention was a solution - not a barrier
<a href="#">Korrell 2000a</a>	Excluded, as trial intervention was a solution - not a barrier
<a href="#">Korrell 2000b</a>	Excluded, as trial intervention was a solution - not a barrier
<a href="#">Liu 2015</a>	Excluded as trial intervention was a solution - not a barrier
<a href="#">Reid 1993</a>	Not an intervention that was sought by the objectives of the review
<a href="#">Reid 1997</a>	Not an intervention that was sought by the objectives of the review
<a href="#">To 1992</a>	Excluded, as no outcomes of interest to this review (fever and need for antibiotics)
<a href="#">Trew 2016</a>	Excluded, as trial intervention was a solution - not a barrier

**DATA AND ANALYSES**
**Comparison 1. Oxidised regenerated cellulose vs no treatment at laparoscopy**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
<a href="#">1 Incidence of adhesions</a>	6		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 De novo	3	360	Odds Ratio (M-H, Fixed, 95% CI)	0.50 [0.30, 0.83]
1.2 Re-formation (or mixture)	3	100	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.07, 0.41]

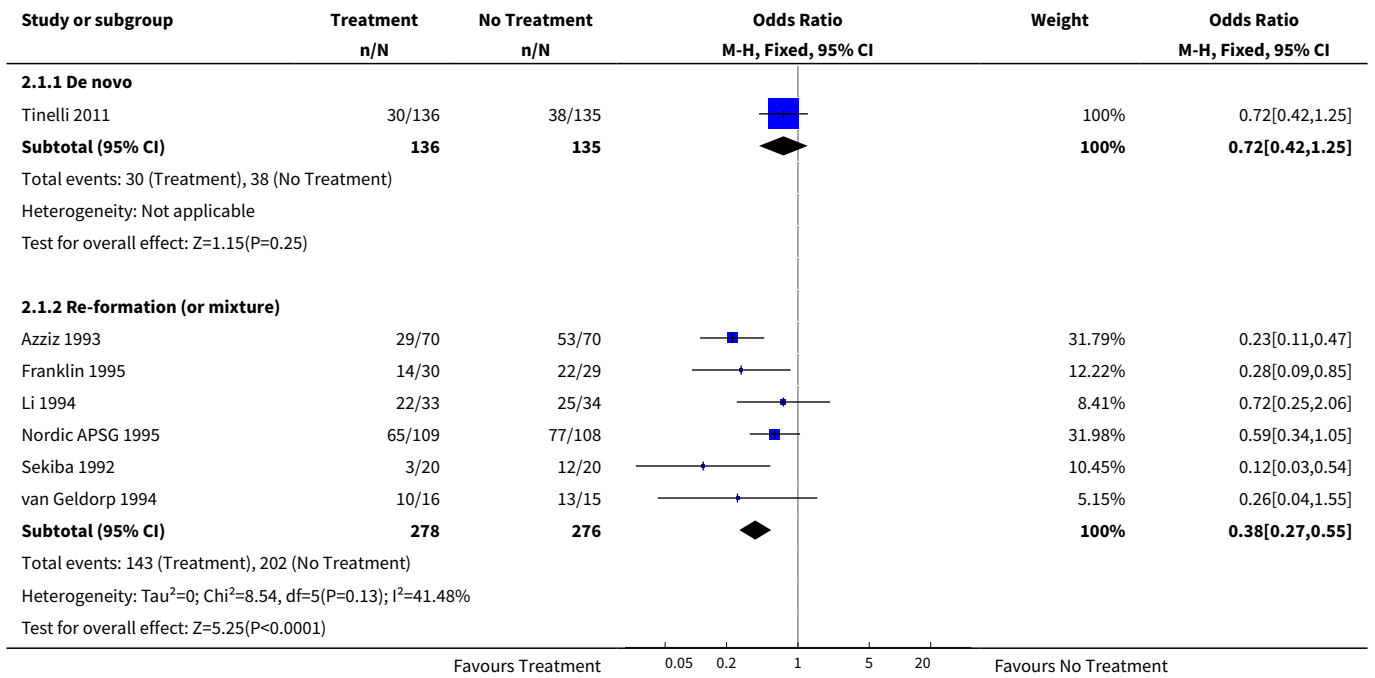
**Analysis 1.1. Comparison 1 Oxidised regenerated cellulose vs no treatment at laparoscopy, Outcome 1 Incidence of adhesions.**



**Comparison 2. Oxidised regenerated cellulose vs no treatment at laparotomy**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of adhesions	7		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 De novo	1	271	Odds Ratio (M-H, Fixed, 95% CI)	0.72 [0.42, 1.25]
1.2 Re-formation (or mixture)	6	554	Odds Ratio (M-H, Fixed, 95% CI)	0.38 [0.27, 0.55]

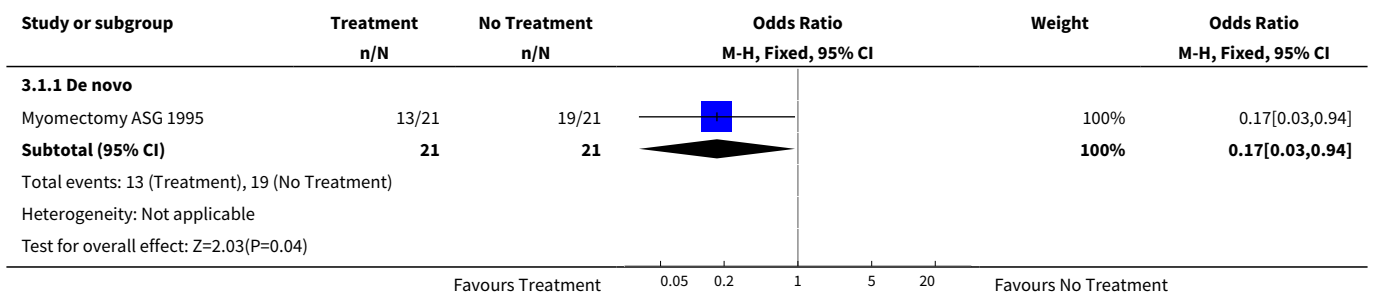
**Analysis 2.1. Comparison 2 Oxidised regenerated cellulose vs no treatment at laparotomy, Outcome 1 Incidence of adhesions.**



**Comparison 3. Expanded polytetrafluoroethylene vs no treatment**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of adhesions	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 De novo	1	42	Odds Ratio (M-H, Fixed, 95% CI)	0.17 [0.03, 0.94]

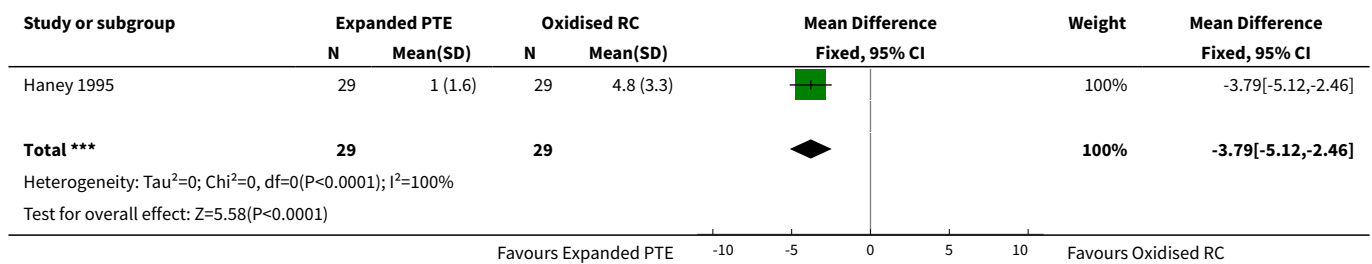
**Analysis 3.1. Comparison 3 Expanded polytetrafluoroethylene vs no treatment, Outcome 1 Incidence of adhesions.**



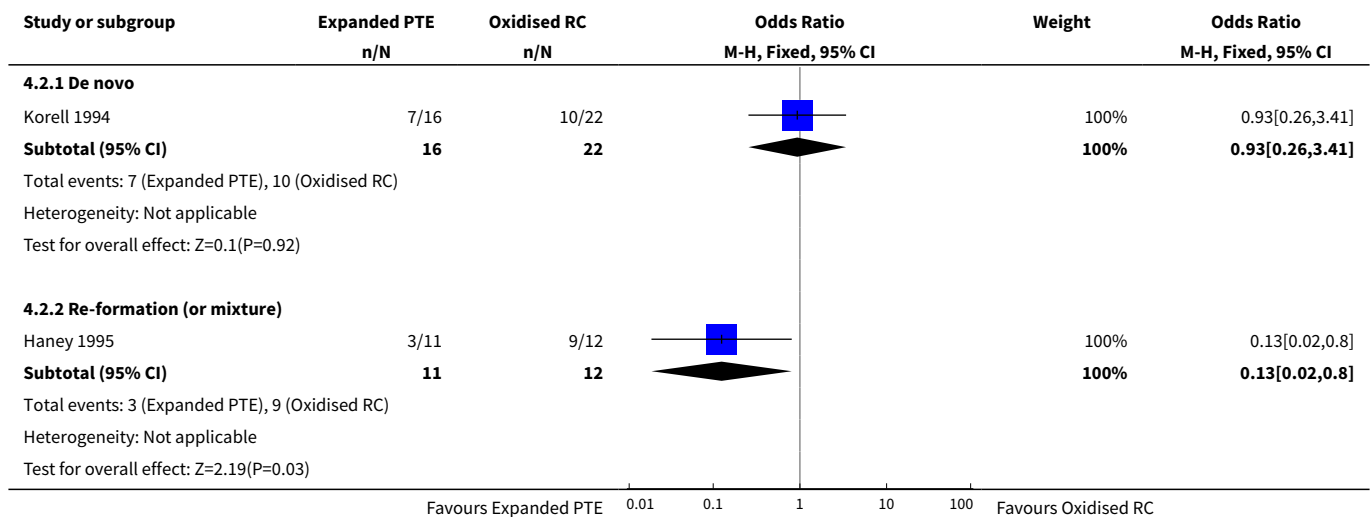
**Comparison 4. Expanded polytetrafluoroethylene vs oxidised regenerated cellulose**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean adhesion score (non-validated score)	1	58	Mean Difference (IV, Fixed, 95% CI)	-3.79 [-5.12, -2.46]
2 Incidence of adhesions	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 De novo	1	38	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.26, 3.41]
2.2 Re-formation (or mixture)	1	23	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.02, 0.80]

**Analysis 4.1. Comparison 4 Expanded polytetrafluoroethylene vs oxidised regenerated cellulose, Outcome 1 Mean adhesion score (non-validated score).**



**Analysis 4.2. Comparison 4 Expanded polytetrafluoroethylene vs oxidised regenerated cellulose, Outcome 2 Incidence of adhesions.**

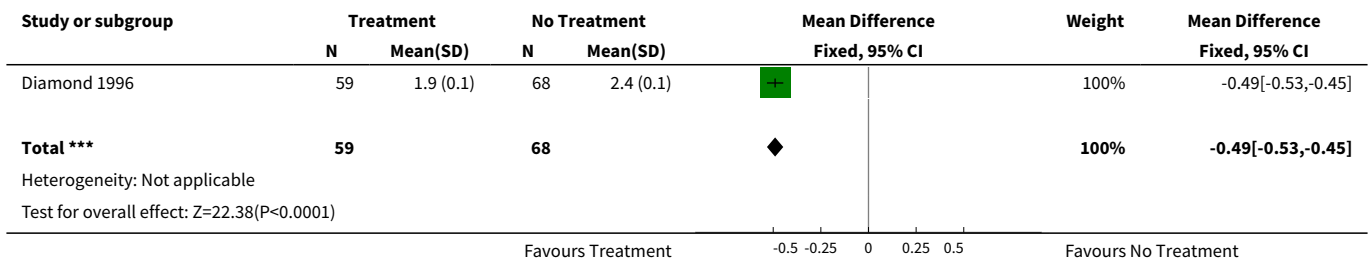




**Comparison 5. Sodium hyaluronate and carboxymethylcellulose vs no treatment**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean adhesion score (non-validated score)	1	127	Mean Difference (IV, Fixed, 95% CI)	-0.49 [-0.53, -0.45]

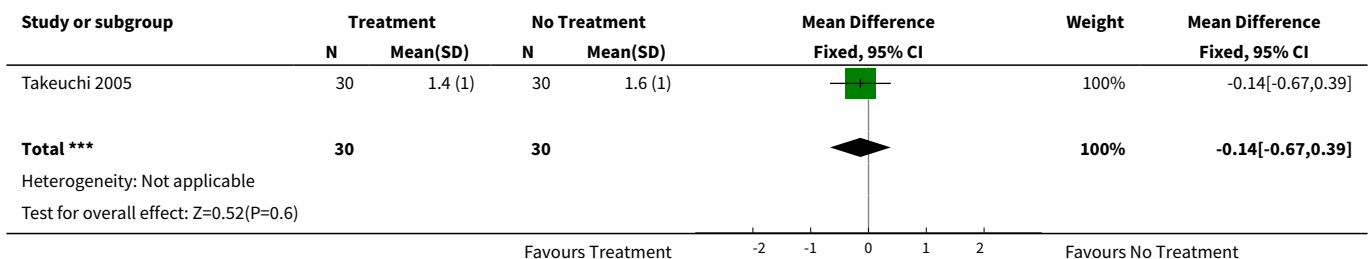
**Analysis 5.1. Comparison 5 Sodium hyaluronate and carboxymethylcellulose vs no treatment, Outcome 1 Mean adhesion score (non-validated score).**



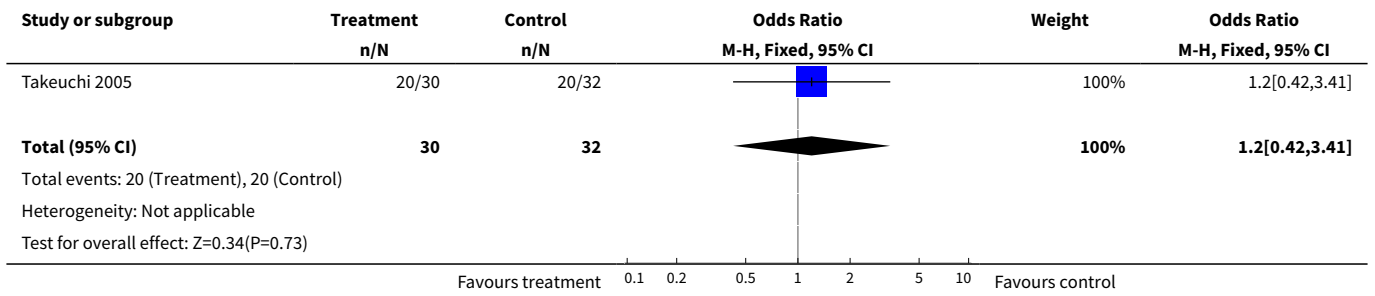
**Comparison 6. Fibrin sheet vs no treatment at laparoscopic myomectomy**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean adhesion score (non-validated score)	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.67, 0.39]
2 Incidence of de novo adhesions per participant	1	62	Odds Ratio (M-H, Fixed, 95% CI)	1.2 [0.42, 3.41]

**Analysis 6.1. Comparison 6 Fibrin sheet vs no treatment at laparoscopic myomectomy, Outcome 1 Mean adhesion score (non-validated score).**



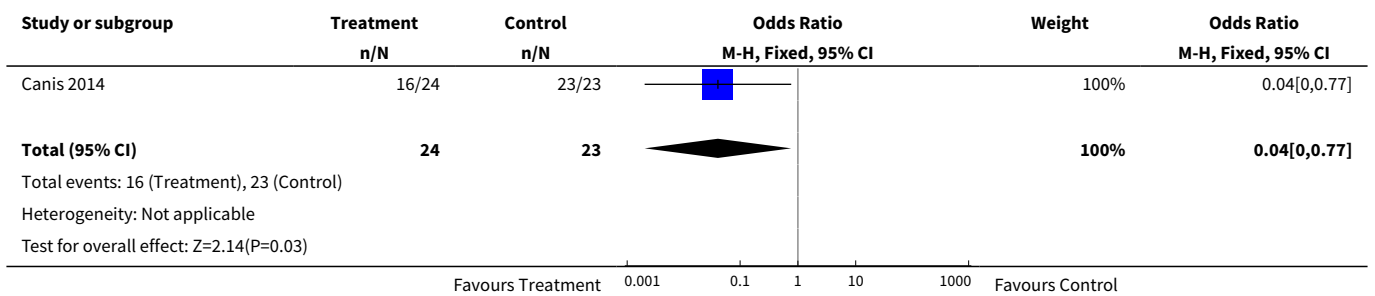
**Analysis 6.2. Comparison 6 Fibrin sheet vs no treatment at laparoscopic myomectomy, Outcome 2 Incidence of de novo adhesions per participant.**



**Comparison 7. Collagen membrane with polyethylene glycol and glycerol vs control at laparotomic myomectomy**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of adhesions	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.04 [0.00, 0.77]
2 Median adhesion score			Other data	No numeric data
3 Clinical pregnancy rate	1	39	Odds Ratio (M-H, Fixed, 95% CI)	5.69 [1.38, 23.48]
4 Ectopic pregnancy rate	1	39	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

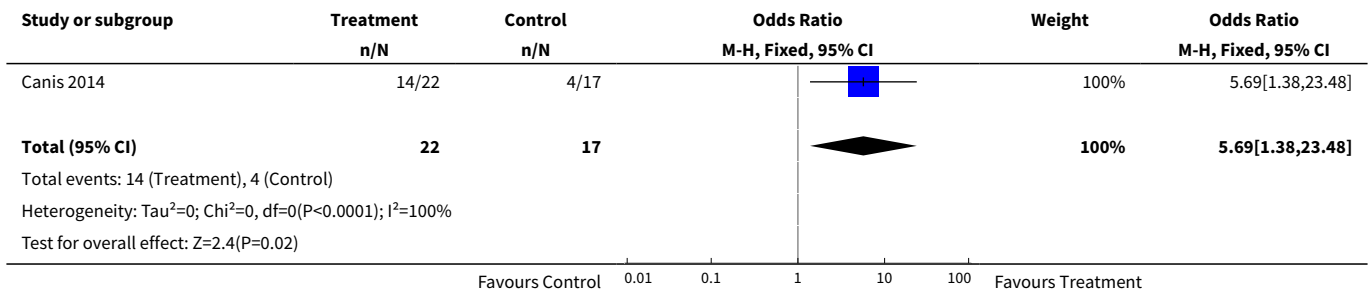
**Analysis 7.1. Comparison 7 Collagen membrane with polyethylene glycol and glycerol vs control at laparotomic myomectomy, Outcome 1 Incidence of adhesions.**



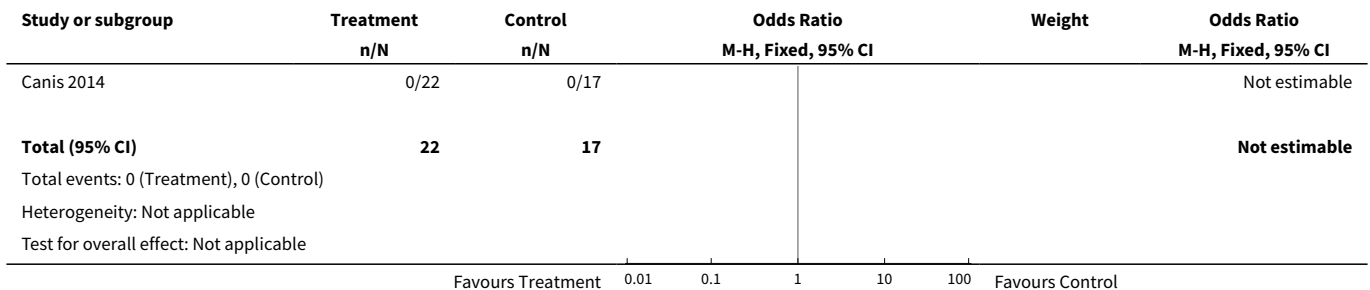
**Analysis 7.2. Comparison 7 Collagen membrane with polyethylene glycol and glycerol vs control at laparotomic myomectomy, Outcome 2 Median adhesion score.**

Study	Median adhesion score Treatment	Median adhesion score Control
Canis 2014	0.8 (n=24)	1.2 (n=23)

**Analysis 7.3. Comparison 7 Collagen membrane with polyethylene glycol and glycerol vs control at laparotomic myomectomy, Outcome 3 Clinical pregnancy rate.**



**Analysis 7.4. Comparison 7 Collagen membrane with polyethylene glycol and glycerol vs control at laparotomic myomectomy, Outcome 4 Ectopic pregnancy rate.**



**APPENDICES**

**Appendix 1. Cochrane Gynaecology and Fertility Group (CGFG) specialised register search strategy**

Procite platform

Searched 21 August 2019

Keywords CONTAINS "adhesion"or "adhesions" or "adhesions outcome" or "gynecologic surgical procedure" or "surgery-gynaecological" or "surgical complications" or "\*Surgical-Procedures,-Laparoscopic" or "post-operative adhesions" or "post operative complications" or "cell adhesion molecules" or"laparoscopic" or"laparoscopy" or"laparotomy"or "myomectomy"or"mini-laparoscopy"or"mini-laparotomy"or"minilaparotomic myomectomy"or"minilaparotomy"or"cystectomy"or"hysterectomy"or"uterine artery embolization"or"UAE"or"pelvic adhesions"or"ovarian adhesions"or"ovarian cystectomy"or"endometrial ablation"or"endometrial adhesions"or"endometrioma" or"electrosurgery"or"electroresection"or"laparotomy"or"\*Laser Surgery"or"salpingectomy"or"\*Salpingostomy-"or"salpingotomy" or Title CONTAINS "adhesion"or "adhesions" or "adhesions outcome"or"surgical complications"or"\*Surgical-Procedures,-Laparoscopic"or"post-operative adhesions"or"endometrial adhesions"or "pelvic adhesions"

AND

Keywords CONTAINS "Barrier Membrane" or "Gore-Tex" or "interceed" or "Polytetrafluoroethylene" or "Seprafilm" or "surgical membrane" or "dextran" or "adhesion barrier" or "adhesion barriers" or "adhesion prevention" or "adhesions outcome" or "surgical membrane" or"Oxiplex"or"SprayGel"or"adept"or "intercoat gel"or"sepraccoat"or "adhesiolysis"or"polyethylene glycol"or"hydrogel"or "intergel" or "adhesions" or"adhesion"or"adhesiolysis"or Title CONTAINS "Barrier Membrane" or "Gore-Tex" or "interceed" or "Polytetrafluoroethylene" or "Seprafilm" or "surgical membrane" or "dextran" or "adhesion barrier" or "adhesion barriers" or "adhesion prevention" or "adhesions outcome" or "surgical membrane" or"Oxiplex"or"SprayGel"or"adept"or "intercoat gel"or"sepraccoat"or "adhesiolysis"or"polyethylene glycol"or"hydrogel"or "intergel"or"adhesions" or"adhesion"or"adhesiolysis" (291 records)

## Appendix 2. CENTRAL search strategy

OID platform

Searched 21 August 2019

- 1 exp gynecologic surgical procedures/ or exp endometrial ablation techniques/ or exp hysterectomy/ or exp hysteroscopy/ or exp ovariectomy/ or exp salpingostomy/ or exp uterine artery embolization/ (4091)
- 2 (gyn\$ adj3 surg\$).tw. (2937)
- 3 exp laparotomy/ (711)
- 4 exp laparoscopy/ (5248)
- 5 laparoscop\$.tw. (17783)
- 6 laparotom\$.tw. (2716)
- 7 (hysterectom\$ or cystoscop\$ or hysteroscop\$).tw. (8399)
- 8 endometrial ablation\$.tw. (285)
- 9 (ovariectom\$ or salpingostom\$).tw. (335)
- 10 (ovar\$ adj2 surg\$).tw. (459)
- 11 (uterine artery embolization or UAE).tw. (527)
- 12 (pelv\$ adj5 surg\$).tw. (1618)
- 13 (ovar\$ adj5 cystect\$).tw. (144)
- 14 endometrioma\$.tw. (282)
- 15 exp endometriosis/ (736)
- 16 endometriosis.tw. (2011)
- 17 fallopian\$.tw. (1099)
- 18 exp Tissue Adhesions/ (431)
- 19 Adhesion\$.tw. (5362)
- 20 myomectomy\$.tw. (682)
- 21 (ovar\$ adj2 defect\$).tw. (8)
- 22 (ovar\$ adj2 cauter\$).tw. (12)
- 23 microsurg\$.tw. (761)
- 24 adhesiolysis.tw. (200)
- 25 electrosurg\$.tw. (377)
- 26 or/1-25 (39827)
- 27 Interceed.tw. (39)
- 28 tc7.tw. (24)
- 29 exp polytetrafluoroethylene/ or exp proplast/ (460)
- 30 (polytetrafluoroethylene\$ or proplast\$).tw. (507)
- 31 (gore-tex or goretex).tw. (102)
- 32 (fibrin adj2 sheet\$).tw. (29)
- 33 (surg\$ adj2 membrane\$).tw. (174)
- 34 exp Cellulose, Oxidized/ (54)
- 35 (Cellulose adj2 Oxidiz\$).tw. (87)
- 36 (Cellulose adj2 Oxidis\$).tw. (11)
- 37 70% dextran\$.tw. (5)
- 38 (fibrin adj2 sealant\$).tw. (422)
- 39 barrier\$.tw. (15131)
- 40 seprafilm\$.tw. (42)
- 41 exp Membranes, Artificial/ (1181)
- 42 (Artificial adj2 Membrane\$).tw. (99)
- 43 (surg\$ adj2 membrane\$).tw. (174)
- 44 (anti adhesi\$ or antiadhesi\$).tw. (177)
- 45 (prevent\$ adj7 adhesi\$).tw. (541)
- 46 (manag\$ adj5 adhesi\$).tw. (102)
- 47 or/27-46 (18089)
- 48 26 and 47 (1136)

## Appendix 3. MEDLINE search strategy

OID platform

Searched from 1946 to 21 August 2019

- 1 exp gynecologic surgical procedures/ or exp endometrial ablation techniques/ or exp hysterectomy/ or exp hysteroscopy/ or exp ovariectomy/ or exp salpingostomy/ or exp uterine artery embolization/ (80533)
- 2 (gyn\$ adj3 surg\$).tw. (10180)
- 3 exp laparotomy/ (18495)
- 4 exp laparoscopy/ (93301)
- 5 laparoscop\$.tw. (119250)
- 6 laparotom\$.tw. (47268)
- 7 (hysterectom\$ or cystoscop\$ or hysteroscop\$).tw. (49659)
- 8 endometrial ablation\$.tw. (1203)
- 9 (ovariectom\$ or salpingostom\$).tw. (27775)
- 10 (ovar\$ adj2 surg\$).tw. (2213)
- 11 (uterine artery embolization or UAE).tw. (4443)
- 12 (pelv\$ adj5 surg\$).tw. (9814)
- 13 (ovar\$ adj5 cystect\$).tw. (667)
- 14 endometrioma\$.tw. (2297)
- 15 exp endometriosis/ (20998)
- 16 endometriosis.tw. (21757)
- 17 fallopian\$.tw. (10049)
- 18 exp Tissue Adhesions/ (12241)
- 19 Adhesion\$.tw. (201767)
- 20 myomectom\$.tw. (3417)
- 21 (ovar\$ adj2 defect\$).tw. (212)
- 22 (ovar\$ adj2 cauter\$).tw. (36)
- 23 microsurg\$.tw. (24576)
- 24 adhesiolysis.tw. (1464)
- 25 electrosurg\$.tw. (3462)
- 26 or/1-25 (545400)
- 27 Interceed.tw. (131)
- 28 tc7.tw. (322)
- 29 exp polytetrafluoroethylene/ or exp proplast/ (11032)
- 30 (polytetrafluoroethylene\$ or proplast\$).tw. (8027)
- 31 (gore-tex or goretex).tw. (2052)
- 32 (fibrin adj2 sheet\$).tw. (121)
- 33 (surg\$ adj2 membrane\$).tw. (737)
- 34 exp Cellulose, Oxidized/ (846)
- 35 (Cellulose adj2 Oxidiz\$).tw. (858)
- 36 (Cellulose adj2 Oxidis\$).tw. (67)
- 37 70% dextran\$.tw. (16)
- 38 (fibrin adj2 sealant\$).tw. (1712)
- 39 barrier\$.tw. (268850)
- 40 seprafilm\$.tw. (223)
- 41 exp Membranes, Artificial/ (97866)
- 42 (Artificial adj2 Membrane\$).tw. (2939)
- 43 (surg\$ adj2 membrane\$).tw. (737)
- 44 (anti adhesi\$ or antiadhesi\$).tw. (3049)
- 45 (prevent\$ adj7 adhesi\$).tw. (6025)
- 46 (manag\$ adj5 adhesi\$).tw. (470)
- 47 or/27-46 (390027)
- 48 26 and 47 (17618)
- 49 randomized controlled trial.pt. (487576)
- 50 controlled clinical trial.pt. (93226)
- 51 randomized.ab. (452140)
- 52 placebo.tw. (205577)
- 53 clinical trials as topic.sh. (188022)
- 54 randomly.ab. (316594)
- 55 trial.ti. (203411)
- 56 (crossover or cross-over or cross over).tw. (81335)
- 57 or/49-56 (1262664)
- 58 (animals not (humans and animals)).sh. (4577069)
- 59 57 not 58 (1160093)
- 60 48 and 59 (759)

## Appendix 4. Embase search strategy

OID platform

Searched from 1980 to 21 August 2019

- 1 exp gynecologic surgery/ or exp pelvis surgery/ or exp uterine tube surgery/ or exp uterus surgery/ (148278)
- 2 exp endometrium ablation/ (2624)
- 3 exp hysterectomy/ or exp abdominal hysterectomy/ or exp vaginal hysterectomy/ or exp radical hysterectomy/ (66175)
- 4 exp hysteroscopy/ (11528)
- 5 exp ovariectomy/ (32790)
- 6 exp salpingoplasty/ or exp salpingostomy/ (1030)
- 7 exp uterine artery embolization/ (3510)
- 8 (gyn\$ adj3 surg\$).tw. (15000)
- 9 exp laparotomy/ (72923)
- 10 exp laparoscopy/ (149397)
- 11 laparoscop\$.tw. (189510)
- 12 laparotom\$.tw. (61388)
- 13 (hysterectom\$ or hysteroscop\$).tw. (61338)
- 14 endometrial ablation technique\$.tw. (90)
- 15 (ovariectom\$ or salpingostom\$).tw. (30291)
- 16 (ovar\$ adj2 surg\$).tw. (3353)
- 17 (uterine artery emboli?ation or UAE).tw. (6932)
- 18 (pelv\$ adj5 surg\$).tw. (16269)
- 19 (ovar\$ adj5 cystect\$).tw. (1342)
- 20 endometrioma\$.tw. (3724)
- 21 exp endometriosis/ (34438)
- 22 endometriosis.tw. (30644)
- 23 fallopian\$.tw. (12290)
- 24 Adhesion\$.tw. (249323)
- 25 myomectom\$.tw. (6030)
- 26 (ovar\$ adj2 defect\$).tw. (282)
- 27 (ovar\$ adj2 cauter\$).tw. (54)
- 28 microsurg\$.tw. (28653)
- 29 adhesiolysis.tw. (2733)
- 30 electrosurg\$.tw. (4356)
- 31 or/1-30 (743178)
- 32 exp oxidized regenerated cellulose/ (1418)
- 33 oxidized regenerated cellulose.tw. (369)
- 34 Interceed.tw. (213)
- 35 tc7.tw. (357)
- 36 exp politef/ (18380)
- 37 (polytetrafluoroethylene\$ or proplast\$).tw. (8747)
- 38 (gore-tex or goretex).tw. (2848)
- 39 (fibrin adj2 sheet\$).tw. (172)
- 40 (surg\$ adj2 membrane\$).tw. (859)
- 41 (Cellulose adj2 Oxidiz\$).tw. (888)
- 42 (Cellulose adj2 Oxidis\$).tw. (85)
- 43 70% dextran\$.tw. (15)
- 44 (fibrin adj2 sealant\$).tw. (2235)
- 45 barrier\$.tw. (326178)
- 46 seprafilm\$.tw. (322)
- 47 exp artificial membrane/ (44422)
- 48 (Artificial adj2 Membrane\$).tw. (3128)
- 49 (surg\$ adj2 membrane\$).tw. (859)
- 50 exp tissue adhesive/ (18874)
- 51 tissue adhesive\$.tw. (1869)
- 52 (prevent\$ adj7 adhesi\$).tw. (7131)
- 53 (anti adhesi\$ or antiadhesi\$).tw. (3717)
- 54 (manag\$ adj5 adhesi\$).tw. (612)
- 55 or/32-54 (421885)
- 56 31 and 55 (24309)

57 Clinical Trial/ (951683)  
 58 Randomized Controlled Trial/ (561335)  
 59 exp randomization/ (83766)  
 60 Single Blind Procedure/ (36208)  
 61 Double Blind Procedure/ (161349)  
 62 Crossover Procedure/ (60191)  
 63 Placebo/ (326256)  
 64 Randomized controlled trial\$.tw. (209043)  
 65 Rct.tw. (33498)  
 66 random allocation.tw. (1900)  
 67 randomly allocated.tw. (33012)  
 68 allocated randomly.tw. (2466)  
 69 (allocated adj2 random).tw. (808)  
 70 Single blind\$.tw. (23173)  
 71 Double blind\$.tw. (194240)  
 72 ((treble or triple) adj blind\$.tw. (988)  
 73 placebo\$.tw. (288978)  
 74 prospective study/ (542433)  
 75 or/57-74 (2066245)  
 76 case study/ (63393)  
 77 case report.tw. (378738)  
 78 abstract report/ or letter/ (1068360)  
 79 or/76-78 (1500676)  
 80 75 not 79 (2014902)  
 81 56 and 80 (1731)

## Appendix 5. PsycINFO search strategy

OID platform

Searched from 1806 to 21 August 2019

1 exp Postsurgical Complications/ (873)  
 2 Adhesion\$.tw. (3445)  
 3 adhesiolysis.tw. (17)  
 4 exp Cell Adhesion Molecules/ (813)  
 5 or/1-4 (4390)  
 6 Interceed.tw. (0)  
 7 (polytetrafluoroethylene\$ or proplast\$.tw. (11)  
 8 (gore-tex or goretex).tw. (5)  
 9 (fibrin adj2 sheet\$.tw. (0)  
 10 (surg\$ adj2 membrane\$.tw. (1)  
 11 (Cellulose adj2 Oxidiz\$.tw. (1)  
 12 dextran\$.tw. (590)  
 13 barrier\$.tw. (66795)  
 14 (Artificial adj2 Membrane\$.tw. (25)  
 15 antiadhesi\$.tw. (5)  
 16 (prevent\$ adj3 adhesion\$.tw. (17)  
 17 anti adhesi\$.tw. (12)  
 18 or/6-17 (67377)  
 19 5 and 18 (238)  
 20 random.tw. (56000)  
 21 control.tw. (429452)  
 22 double-blind.tw. (22320)  
 23 clinical trials/ (11415)  
 24 placebo/ (5327)  
 25 exp Treatment/ (1011240)  
 26 or/20-25 (1395394)  
 27 19 and 26 (75)

## WHAT'S NEW



Date	Event	Description
13 September 2019	New search has been performed	Review has been updated; 1 new study has been included ( <a href="#">Canis 2014</a> )
13 September 2019	New citation required but conclusions have not changed	Evidence regarding new interventions has been included; however due to low-quality evidence, we made no changes to our overall conclusions at this update

## HISTORY

Protocol first published: Issue 3, 1996

Review first published: Issue 1, 1999

Date	Event	Description
19 March 2015	New search has been performed	Review has been updated; 1 new study has been included ( <a href="#">Tinelli 2011</a> )
19 March 2015	New citation required but conclusions have not changed	We made no change to our conclusions at this update
2 June 2008	Amended	Review has been converted to new review format
20 December 2007	New citation required and conclusions have changed	Substantive amendments have been made
20 December 2007	New search has been performed	Review has been updated

## CONTRIBUTIONS OF AUTHORS

In the 2020 update, contributions of the review authors included the following.

1. Gaiyy Ahmad (GA).
  - a. Main review author of the 2020 update; undertook search, screened search results, organised retrieval of papers, screened papers against inclusion criteria, extracted data from papers, managed and interpreted data, and supervised KK, PA, and MT throughout the process.
2. Kyungmin Kim (KK).
  - a. Co-review author of the 2020 update; organised retrieval of papers, screened papers against inclusion criteria, extracted data from papers, and managed and interpreted data.
3. Matthew Thompson (MT).
  - a. Co-review author of the 2020 update; organised retrieval of papers, screened papers against inclusion criteria, extracted data from papers, and managed and interpreted data.
4. Priya Agarwal (PA).
  - a. Co-review author of the 2020 update; organised retrieval of papers, screened papers against inclusion criteria, extracted data from papers, and managed and interpreted data.
5. Helena O'Flynn (HO'F).
  - a. Co-review author of the 2015 update; assisted with writing of the 2020 update.
6. Akshay Hindocha (AH).
  - a. Co-review author of the 2015 update; assisted with writing of the 2020 update.
7. Andrew Watson (AW).
  - a. Co-review author of the 2015 update; assisted with writing of the 2020 update.

## DECLARATIONS OF INTEREST

Previous review author David Wiseman is a past employee of Ethicon Limited (manufacturer of oxidised regenerated cellulose) and is now a consultant to several companies, including Ethicon.

AW received a consultancy fee and lecture fees from the distributors of Adept in 2003.

GA, KK, MT, PA, HO'F and AH have no interests to declare and received no external funding.

## SOURCES OF SUPPORT

### Internal sources

- University of Auckland, New Zealand.

### External sources

- Yorkshire Regional Health Authority - Research & Development Unit, Other.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

At the 2015 update:

1. the analysis method was changed from Peto ORs to Mantel-Haenszel ORs; and
2. the outcomes of "improvement of adhesion score at SLL" and "worsening of adhesion score at SLL/mean adhesion score at SLL" were combined in the text for ease of presentation. This did not affect the analysis nor the conclusions of this review.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Cellulose, Oxidized [\*therapeutic use]; Cervix Uteri [surgery]; Collagen [administration & dosage]; Fibrin [administration & dosage]; Glycerol [administration & dosage]; Hyaluronic Acid [administration & dosage]; Incidence; Infertility, Female [\*surgery]; Laparoscopy [adverse effects]; Laparotomy [adverse effects]; Membranes, Artificial; Pain, Postoperative [prevention & control]; Pelvis [surgery]; Polyethylene Glycols [administration & dosage]; Polytetrafluoroethylene [\*administration & dosage]; Postoperative Complications [epidemiology] [\*prevention & control]; Pregnancy Rate; Randomized Controlled Trials as Topic; Second-Look Surgery; Tissue Adhesions [epidemiology] [prevention & control]; Viscosupplements [administration & dosage]

### MeSH check words

Female; Humans; Pregnancy