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Preventing adhesions in laparoscopic surgery: the role of anti-adhesion agents

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Key content

- Surgical injury causes the release of cytokines, growth factors, cell adhesion molecules and histamine, creating an inflammatory response, which can lead to adhesion formation in the peritoneal cavity.
- Compared with open surgery, laparoscopy reduces the risk of adhesion formation, but the risk is not completely eliminated.
- Adhesion formation is multifactorial and depends on patient healing, surgical technique and equipment factors.
- Adhesions after gynaecological surgery can have long-term consequences including small bowel obstruction, chronic pelvic pain, deep dyspareunia and female subfertility.
- There are a variety of anti-adhesion agents with different properties available for use in laparoscopic surgery.

Learning objectives

- To review the pathophysiology of adhesion formation after laparoscopic surgery.
- To identify which anti-adhesive agents are currently available in clinical practice.
- To understand the mechanism by which adhesion prevention agents work.
- To review the effectiveness and cost implications of anti-adhesive agents.

Ethical issues

- Given the extra cost of anti-adhesive agents, and the limited information regarding their efficacy, should surgeons be using them in laparoscopic gynaecological surgery?
- Is the use of anti-adhesion agents complementary or detrimental to meticulous surgical technique?

Keywords: laparoscopy / prevention and control / tissue adhesions

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Introduction

The development of peritoneal adhesions following surgery is a complication that can have a significant impact on patients and the wider healthcare system. It is estimated that adhesions may develop in up to 90% of patients undergoing major abdominal surgery and 55–100% of women undergoing pelvic surgery.[1]

Adhesions may occur following either open or laparoscopic surgery. Although most patients are asymptomatic, adhesions can be associated with significant morbidity including small bowel obstruction, chronic pelvic pain, deep dyspareunia and female subfertility.[2] In addition, adhesions may increase the risk of complications during subsequent surgery, including problems relating to difficult abdominal access, increased blood loss and increased duration of surgery.[3–5] In a large study of gynaecological pelvic surgery performed in Scotland, the readmission rate related to adhesions was 13.9%.[6]

Quantifying the cost of adhesion-related problems is difficult. In the USA, where litigation rates are high and the costs of health care great, the estimated yearly costs of managing adhesion-related complications exceed $2 billion.[7] In the UK, in a study from 2002, it was estimated that the direct cost of readmissions related to adhesions in the first year after lower abdominal surgery is £24.2 million, which increases to £95.2 million 10 years after the initial surgery.[8] Therefore, minimising the formation of adhesions during gynaecological surgery is paramount.

In the first instance, the prevention of surgical adhesions relies on meticulous surgical technique, further enhanced with the use of a minimally invasive surgical approach where possible. Despite these important steps, a significant risk of adhesion formation remains. A variety of additional

approaches have been used in the past: from agents to prevent fibrin formation (sodium citrate and anticoagulants), to fibrinolytic agents such as streptokinase and the insertion of inert silicones at the time of surgery.[9] Several novel anti-adhesive agents have been developed, which are proposed to be safe and effective adjuncts to good surgical technique.

This article describes the pathophysiology of adhesion formation after surgery, presenting a summary of the main anti-adhesive agents available in the market, an overview of the current studies on their effectiveness and an evaluation of the cost implications of their use in the healthcare system.

Pathophysiology

Adhesion formation is multifactorial and depends on patient healing (peritoneal repair), surgical technique and equipment factors.

The inciting event for adhesion formation is injury to the peritoneal mesothelium, which initiates a peritoneal repair response. Subsequently, the development of adhesions depends on the balance between fibrin deposition and degradation (fibrinolysis) that begins within hours of surgery.[9] Factors that favour the deposition of fibrin over its degradation will lead to the development of a bridging fibrinous mass between adjacent peritoneal surfaces. Specifically, the organisation of fibrin into adhesions is potentiated by two risk factors associated with surgical injury: inflammation and tissue ischaemia.[9]

At a biomolecular level, this injury causes damaged tissues to release cytokines, growth factors, cell adhesion molecules and histamine, which mediate a local inflammatory response that promotes fibrin deposition.[10] This inflammatory reaction involves processes such as coagulation and the recruitment of leucocytes (macrophages and neutrophils) and fibroblasts.[11,12] In particular, macrophages are involved in the recruitment of adjacent mesothelial cells and fibroblasts, which migrate to the site of peritoneal injury and re-epithelialise the injured peritoneal surface over 3–5 days.[10] Figure 1 illustrates the pathway of adhesion formation.

Adhesion formation also occurs within this 3–5-day window, which has clinical implications for the efficacy of anti-adhesion agents that must also be active over this period.[10]

Furthermore, contamination of the peritoneal cavity with materials such as sutures, talcum powder, starch, faeces or bacteria may induce further inflammation, which inhibits fibrinolysis and increases the likelihood of adhesion formation. Therefore, minimising tissue injury and preventing post-operative infection and peritoneal contamination is important for preventing adhesions after laparoscopic surgery.[13]

Tissue damage associated with ischaemia also promotes the formation of peritoneal adhesions as a maladaptive response. The inflammatory response to injury develops to revascularise areas of relative ischaemia following surgical procedures that may have disrupted tissue vasculature, such as fulguration, ligation or crushing.[2]

Adhesion prevention methods

Measures for preventing adhesion development may include minimising injury, preventing coagulation of serous exudate, introducing a physical barrier between peritoneal surfaces and inhibiting the cellular response to tissue injury (fibroblasts and macrophages).[10]

Adhesion prevention measures can thus be classified into meticulous surgical technique, physical barrier agents (liquid or solid) and pharmacological agents. Figure 2 summarises the measures available for adhesion prevention.

Meticulous surgical technique

Best practice surgical technique is the gold standard measure against adhesion development. The principles of meticulous surgical technique include tissue handling minimisation and prevention of thermal injury, optimised haemostasis, maintaining a moist surgical field, strict infection control and avoiding contamination through copious irrigation and unnecessary foreign material use (such as talcum powder).[10,14]

Laparoscopy versus laparotomy

Minimal access techniques should be chosen over laparotomy wherever possible as a method of reducing adhesion formation. Laparoscopy involves smaller abdominal incisions, less handling of peritoneal tissues and reduced exposure to foreign materials.[15] Hence, laparoscopy ultimately reduces the rate of adhesions over open surgery.[16–19] Buletti et al.[20] showed significantly lower adhesion rates at second-look laparoscopy when directly comparing laparotomy and laparoscopy. Despite this, laparoscopy does not guarantee complete adhesion prevention, especially in conditions that are at high risk of adhesion formation, such as endometriosis or chronic pelvic inflammatory disease.[10] There is also evidence that, despite reducing de novo adhesions, laparoscopy may not reduce adhesion reformation.[20] In contrast, animal studies have suggested that perhaps a carbon dioxide pneumoperitoneum may in fact cause peritoneal inflammation and thus it has been suggested that a combination of a low temperature, humidified gas mixture of carbon dioxide, nitrous oxide and oxygen is the best way to reduce this.[20]

Physical barrier agents

Physical barrier agents are inert materials that exert their anti-adhesive effects by separating opposing injured

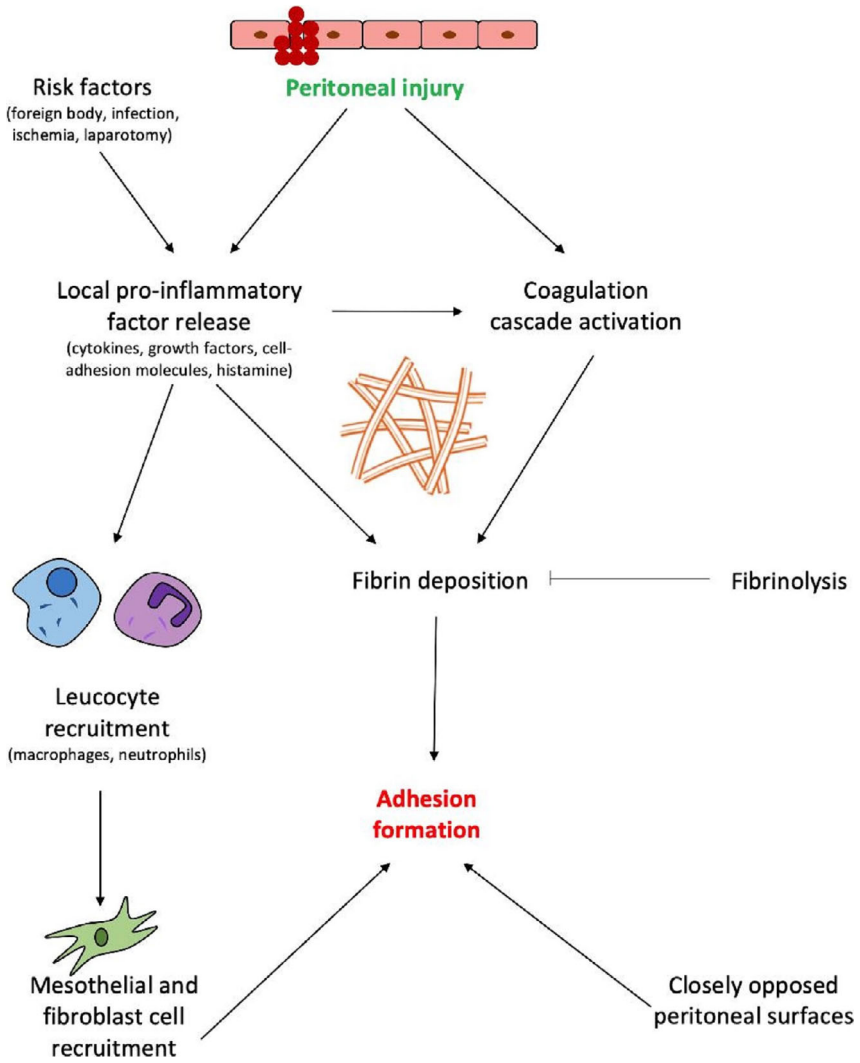

Figure 1. Pathophysiology of adhesion formation.

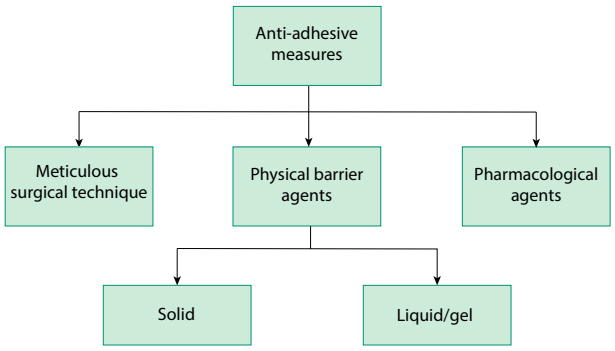

Figure 2. Classification of anti-adhesive measures.

peritoneal surfaces during tissue healing.[10] In particular, barrier agents act to separate peritoneal surfaces for longer than 3 days during the peak time of mesothelial re-epithelialisation to prevent adhesion formation. In addition, each agent is present temporarily by virtue of absorption, resorption, degradation or surgical removal.[10]

Although many physical barrier agents have been developed, only a few are used regularly in clinical practice. Barrier agents can be subdivided into solid or liquid barrier agents. Generally, solid barrier agents are used more frequently in open surgery, while liquid or gel barriers are favoured in laparoscopy. Figure 3 demonstrates the classification and types of physical barrier agents available.

Oxidised regenerated cellulose (Gynecare Interceed™ – Johnson & Johnson, Somerville, NJ)

Oxidised regenerated cellulose (ORC) is an absorbable synthetic sheet that can be applied directly on to damaged peritoneum, thus acting as a mechanical barrier (Figure 4). The sheet may be cut as required, allowing for its use in

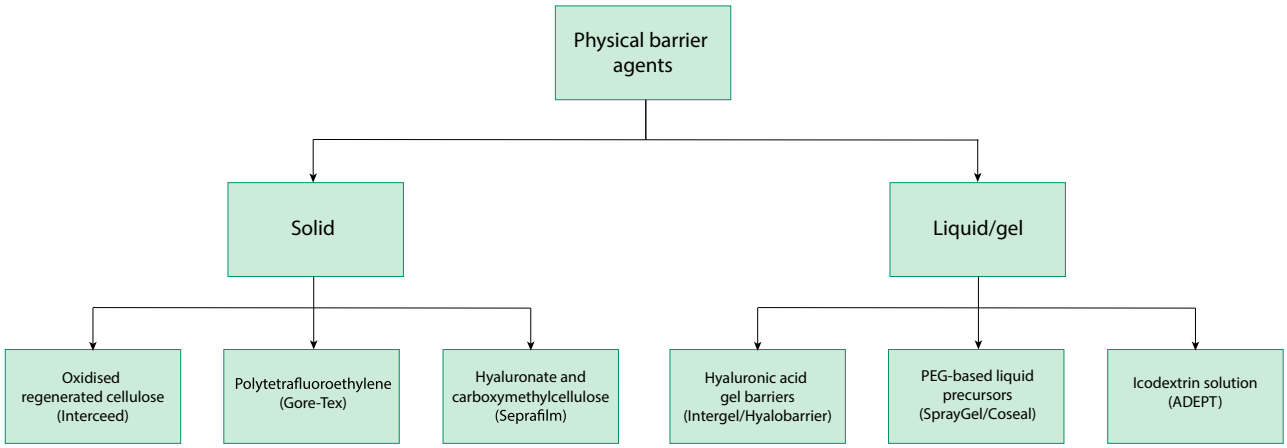

Figure 3. Classification and types of physical barrier agents.

laparoscopic and open surgery.[21,22] On application, the ORC sheet transforms into a gel that coats the peritoneal surface and is completely absorbed within 2 weeks.[23] Importantly, optimal haemostasis must be achieved before the application of the ORC sheet, as the mixture of blood with ORC increases fibrin deposition and may increase the formation of adhesions.[24] ORC was trialled in the USA for patients at high risk of developing postoperative adhesions after gynaecologic pelvic laparotomy.[10] However, it is often used in laparoscopic surgery.[25] No adverse effects have been reported with the use of ORC.[2]

Numerous randomised controlled trials (RCTs) have been conducted comparing the use of ORC versus no barrier agent. In a meta-analysis of 12 RCTs, ORC used in laparoscopy was associated with a reduced incidence (odds ratio [OR] 0.30, 95% confidence interval [CI] 0.12–0.79) and recurrence (OR 0.19, 95% CI 0.09–0.42) of adhesions when compared with no barrier treatment.[26] In addition, a pooled estimate of three trials comparing ORC with no barrier agent found that ORC significantly reduced the risk of adhesions (relative risk [RR] 0.51, 95% CI 0.31–0.86).[27]

Polytetrafluoroethylene (Gore-Tex® – W.L. Gore & Associates, Inc., Flagstaff, AZ, USA)

Polytetrafluoroethylene (PTFE) is a flexible non-absorbable membrane that must be sutured on to peritoneal surfaces and requires a secondary surgical procedure for its removal (Figure 5).[2] Therefore, the need for suturing and subsequent removal renders PTFE an undesirable anti-adhesive agent. In particular, the requirement of suturing the PTFE into place may lead to surgical delays, especially in laparoscopic surgery.[2]

To date, the use of PTFE physical barriers has only been evaluated in the context of open surgery and there is no evidence for its use in laparoscopic surgery.

Chemically modified sodium hyaluronate–carboxymethylcellulose (Seprafilm® – Genzyme Corporation, Cambridge, MA, USA)

Hyaluronic acid is an anionic linear polysaccharide composed of sodium D-glucuronate and N-acetyl-D-glucosamine. Hyaluronic acid sheets are absorbable membranes composed of two synthetic polysaccharides:

Figure 4. Gynecare Interceed™ – Oxidised regenerated cellulose. Reproduced with permission of Ethicon US, LLC.

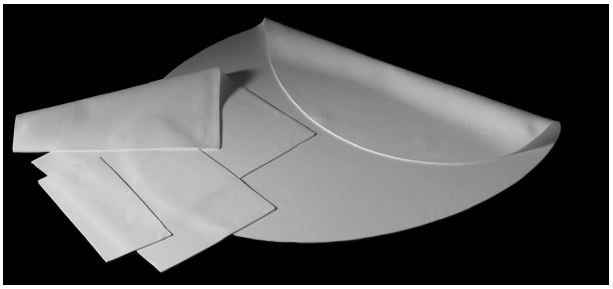

Figure 5. Gore-Tex® – Polytetrafluoroethylene. Reproduced with permission of W.L. Gore & Associates, Inc.

chemically modified sodium hyaluronate and carboxymethylcellulose. Within 24–48 hours of application, the membrane becomes a gelatinous barrier that prevents the juxtaposition of damaged peritoneal tissues and is absorbed within 7 days.[2]

The effectiveness of hyaluronic acid sheets has mostly been demonstrated in non-gynaecological surgery. In terms of gynaecological surgery, one RCT of 127 patients evaluated the efficacy of hyaluronic acid sheets in open myomectomy compared with no treatment.[26] The results concluded that the intervention group experienced a reduction in the incidence, extent and severity of adhesion formation at second-look laparoscopy compared with no treatment. However, a Cochrane systematic review in 2008[26] criticised the statistical analyses used in the study, and the results should be interpreted with caution. No adverse effects have been reported with the use of hyaluronic acid sheets.[2]

Currently, hyaluronic acid sheets are indicated for patients at high risk of developing adhesions after abdominal or pelvic laparotomy in the USA.[10] The membrane is brittle and tends to break when manipulated, making it unsuitable for laparoscopic application.[2] However, hyaluronic acid sheets can be used in laparoscopy by creating a solution of Seprafilm mixed with normal saline and then flushing the solution through one of the laparoscopic ports using a catheter (Figure 6).[2] The solution coats the peritoneal surface with a gelatinous membrane which prevents adhesions from other surfaces. Despite this, there has been insufficient evidence to support the use of hyaluronic acid sheets in laparoscopy using this method.[2]

Figure 6. Seprafilm® – Chemically modified sodium hyaluronate–carboxymethylcellulose. Reproduced from Haensig et al.,[41] with permission of Dovepress.

Figure 7. Hyalobarrier® – Hyaluronic acid gel barriers. Reproduced with permission of Anika Therapeutics, Inc.

Hyaluronic acid liquid barriers (Hyalobarrier® – Anika Therapeutics, Bedford, MA, USA)

Hyaluronic acid also exists in the form of gel barriers, which have been found to be effective in both laparoscopy and open surgery (Figure 7). A meta-analysis of four RCTs comparing hyaluronic acid liquid barriers with placebo demonstrated that the use of hyaluronic acid agents may decrease adhesion formation (OR 0.31, 95% CI 0.19–0.51).[29] In addition, a subsequent meta-analysis of five RCTs showed a significant reduction in intraperitoneal adhesions after laparoscopic surgery (OR 0.25, 95% CI 0.09–0.63) and in intrauterine adhesions after hysteroscopic surgery (OR 0.41, 95% CI 0.217–0.766) with the use of auto cross-linked hyaluronan gel.[30]

Polyethylene glycol (PEG)-based liquid adhesion barrier (SprayGel® – Confluent Surgical Inc., Waltham, MA, USA) (Coseal sealant – Baxter Healthcare Corporation, Deerfield, IL, USA)

The polyethylene glycol (PEG) adhesion barrier is a synthetic hydrogel that is sprayed on to target tissues to form a gelatinous barrier that remains intact for 5–7 days before being absorbed from the peritoneal cavity after 30 days.[31] Coseal is well known as an effective anti-adhesive agent in the context of cardiothoracic surgery but is currently being trialled as an anti-adhesive in gynaecological surgery.[32]

The evidence regarding the efficacy of PEG adhesion barriers in the setting of laparoscopy and open surgery is conflicting. A meta-analysis of three RCTs in 2012 demonstrated a significant reduction in the incidence of adhesion development with the use of PEG-based barriers in fertility-conserving laparoscopic gynaecological surgery (OR 0.27, 95% CI 0.11–0.67).[33] However, a 2014 systematic review of four trials showed no significant difference in the incidence of adhesion formation in laparoscopic and open procedures when comparing PEG-based barriers with no

treatment, although adhesion scores were lower in those who received PEG.[27]

Icodextrin solution (ADEPT® – Baxter Healthcare Corporation, Deerfield, IL, USA)

Icodextrin solution is used as an iso-osmolar surgical irrigant and is composed of a 4% alpha-1,4 glucose polymer solution that persists on peritoneal surfaces. A fluid reservoir of the icodextrin solution is left in the peritoneal cavity after surgery and is slowly absorbed via the lymphatic system over a period of 4 days.[34] Therefore, the solution acts to separate injured serosal surfaces during the period of peritoneal healing (Figure 8).

Evidence for 4% icodextrin solution in laparoscopic surgery remains conflicted. However, it is the only agent in the USA approved by the Food and Drug Administration for preventing peritoneal adhesions in gynaecologic laparoscopy. In a US trial involving laparoscopic adhesiolysis in 402 patients, the use of 4% icodextrin solution led to a 9.8% reduction in the incidence of adhesion development compared with controls on second-look laparoscopy.[34] However, a meta-analysis of four RCTs comparing icodextrin with no treatment or Hartmann's solution showed that icodextrin decreased the incidence of small bowel obstruction (2% versus 11%), but did not reduce adhesion formation or the need for reoperation for adhesive bowel obstruction (RR 0.33, 95% CI 0.03–3.11).[27] There have been case studies concerning possible extravasation of ADEPT, resulting in return to theatre but the authors of one article suggest that these cases can be managed conservatively and the occurrence reduced by meticulous suturing at the port sites.[35]

Another interesting hypothesis that requires further research is that to separate the peritoneal surfaces, organs may be required to float within the solution. A small study by Carpenter et al.[36] demonstrated that ovaries did not float in the commonly used solutions for hydrofloatation, and the authors concluded that it would be unlikely that these solutions would prevent re-adherence of ovaries to the pelvic side wall after endometriosis surgery.

Table 1 gives a summary of the anti-adhesion agents discussed.

Figure 8. ADEPT® – Icodextrin solution. Reproduced with permission of Baxter Australia Inc and Enso Creative Communications.

Pharmacological agents

Corticosteroids

Given that adhesion formation involves inflammation, corticosteroids have been trialled to dampen the post-surgical inflammatory response to prevent adhesions. However, the use of corticosteroids as an anti-adhesive agent is not supported by current evidence. A meta-analysis of five RCTs that investigated the efficacy of steroids in preventing adhesions following open gynaecological surgery demonstrated a failure to reduce adhesion formation or improve pregnancy rates.[29]

Heparin

Heparin has not been shown to be useful in adhesion prevention. In a study by Reid et al.[37] adding heparin to oxidised regenerated cellulose did not confer any benefit in postoperative adhesion formation.

Complications associated with adhesion barriers

A 2016 study by Tulandi et al.[38] reviewed the use of adhesion barriers in myomectomy or hysterectomy and the complications in the immediate postoperative period. The authors looked at laparoscopy and laparotomy, with the most commonly used adhesion barriers being sodium hyaluronate–carboxymethylcellulose and oxidised regenerated cellulose. Adhesion barriers were only used in 1.9% of the cases reviewed, suggesting that most gynaecologists did not perceive the importance of postoperative adhesion. The review concluded that the use of an adhesion barrier was not without complications of ileus and possible bowel obstruction (more so in the laparotomy group), but the incidence of these complications was low.

Cost implications

Postoperative adhesions impose a considerable economic burden on healthcare systems worldwide. In particular, complications related to adhesions increase surgical workload and hospital expenditure and divert funds away from other healthcare services.[8] However, the widespread introduction of anti-adhesive agents would also incur significant costs for healthcare systems, including the cost of the agent and the increase in operative time required for its use.

Table 1. Summary of anti-adhesive barrier methods

Type of barrier	Trade name	Cost per unit	Mechanism of action	Evidence	Countries approved	
					Europe#	US
Oxidised regenerated cellulose	Interceed	£125 to £200*	Solid sheet transforms into gel to coat peritoneum	Meta-analysis of 12 RCTs – reduced incidence (OR 0.30) and recurrence of adhesions (OR 0.19) Meta-analysis of 3 trials – reduced risk of adhesions (RR 0.51)	Yes	Yes (Open)
PFTE	Gore-Tex	–	Non-absorbable solid membrane sutured on to peritoneum	Limited gynaecological evidence in laparoscopic surgery	Yes	No
Hyaluronic acid sheets	Seprafilm	£170*	Sheets form gelatinous solid barrier on peritoneum	Limited gynaecological evidence RCT of 127 patients – reduced incidence, extent and severity of adhesions	Yes	Yes (Open)
Hyaluronic acid gel	Hyalobarrier	£124 per 10 ml**	Highly viscous gel coats peritoneum	Meta-analysis of 4 RCTs – reduced adhesions (OR 0.31) Meta-analysis of 5 RCTs – reduced adhesions in laparoscopy (OR 0.25) and in hysteroscopy (OR 0.41)	Yes	No
PEG-based liquid barrier	SprayGel Coseal	£115 per 2 ml (Coseal)*	Sprayed on to peritoneal surfaces to form gel barrier	Conflicting evidence Meta-analysis of 3 RCTs – reduced incidence of adhesions (OR 0.27) Systematic review of 4 trials failed to show difference in adhesion formation	Yes	No
Icodextrin solution	ADEPT	£140 per 1500 ml*	Solution reservoir left in peritoneal cavity to separate peritoneal surfaces	Conflicting evidence RCT of 402 patients – reduced adhesions by 9.8% Meta-analysis of 4 RCTs – no reduction in adhesions	Yes	Yes (Lap)

*Price as per company and conversion from US dollars to pounds December 2017. **Price as per company and conversion from Euros to pounds December 2017. #Approved in at least one country.
Lap = laparoscopy; Open = open surgery; PEG = polyethylene glycol; PFTE = polytetrafluoroethylene; RCT = randomised controlled trial.

Studies on the cost-effectiveness of anti-adhesives are limited and most cost analyses were performed more than 10 years ago. In 2007 a study investigating cost-effectiveness involving financial modelling over a 10-year period between 1986 and 1995 found that anti-adhesives costing up to €130 and with 25% efficacy could save €40 million.[39] A study in 2011, which was financially modelled based on the 'payment by results' system in England, showed that the implementation of effective anti-adhesive agents costing approximately £110 per product, which results in a 25% reduction in adhesion prevalence, could have made approximately £700,000 in cost savings for the NHS during 2004–2008.[40] Despite these estimated cost benefits, not many anti-adhesive agents currently available demonstrate this level of clinical efficacy or fall within this price range.

Conclusion

Optimised adhesion prevention has the potential to significantly reduce healthcare costs and patient morbidity following laparoscopic abdominal or pelvic surgery. Currently, the gold-standard anti-adhesive measure is meticulous surgical technique, which should be adopted by all surgeons. At present, liquid anti-adhesive agents are easier to use than solid agents in laparoscopic surgery, with 4% icodextrin solution the only liquid anti-adhesive agent recommended under US guidelines.

Overall, the evidence for the efficacy of anti-adhesive agents in laparoscopic procedures is limited, which has prevented their widespread uptake in gynaecological surgery. In particular, evidence for improved clinical outcomes, such as the incidence of chronic pelvic pain, infertility and bowel obstruction, is lacking. It must be noted, however, that there is difficulty in producing level A evidence. Second-look operations are invasive and the alternative of ultrasound to detect adhesions requires significant expertise with a limited sensitivity and specificity.

Further investigation is required to evaluate the long-term clinical outcomes associated with the use of anti-adhesive agents. Additional high-quality cost–benefit analyses are

required before the routine use of anti-adhesive agents can be recommended in the UK.

Disclosure of interests
There are no conflicts of interest.

Contribution to authorship
MA-A instigated and wrote the article; TP researched and wrote the first draft of the article; AA edited the article. All authors approved the final version.

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References

1 Liakakos T, Thomakos N, Fine PM, Dervenis C, Young RL. Peritoneal adhesions: etiology, pathophysiology, and clinical significance. Recent advances in prevention and management. *Dig Surg* 2001;**18**(4):260–73.
2 Robertson D, Lefebvre G. Adhesion prevention in gynaecological surgery. *J Obstet Gynaecol Can* 2010;**32**(6):598–602.
3 ten Broek RP, Schreinemacher MH, Jilesen AP, Bouvy N, Bleichrodt RP, van Goor H. Enterotomy risk in abdominal wall repair: a prospective study. *Ann Surg* 2012;**256**(2):280–7.
4 ten Broek RP, Strik C, Issa Y, Bleichrodt RP, van Goor H. Adhesiolysis-related morbidity in abdominal surgery. *Ann Surg* 2013;**258**(1):98–106.
5 Van Der Krabben AA, Dijkstra FR, Nieuwenhuijzen M, Reijnen MM, Schaapveld M, Van Goor H. Morbidity and mortality of inadvertent enterotomy during adhesiotomy. *Br J Surg* 2000;**87**(4):467–71.
6 Lower AM, Hawthorn RJ, Clark D, Boyd JH, Finlayson AR, Knight AD, et al. Adhesion-related readmissions following gynaecological laparoscopy or laparotomy in Scotland: an epidemiological study of 24 046 patients. *Hum Reprod* 2004;**19**(8):1877–85.
7 Sikirica V, Bapat B, Candrilli SD, Davis KL, Wilson M, Johns A. The inpatient burden of abdominal and gynecological adhesiolysis in the US. *BMC Surg* 2011;**11**:13.
8 Wilson MS, Menzies D, Knight AD, Crowe AM. Demonstrating the clinical and cost effectiveness of adhesion reduction strategies. *Colorectal Dis* 2002;**4**(5):355–60.
9 Ellis H. The causes and prevention of intestinal adhesions. *Br J Surg* 1982;**69** (5):241–3.
10 Diamond MP. Reduction of postoperative adhesion development. *Fertil Steril* 2016;**106**(5):994–7.e1.
11 Attard JA, MacLean AR. Adhesive small bowel obstruction: epidemiology, biology and prevention. *Can J Surg* 2007;**50**(4):291–300.
12 diZerega GS. Biochemical events in peritoneal tissue repair. *Eur J Surg Suppl* 1997;(**577**):10–6.
13 Luijendijk RW, de Lange DC, Wauters CC, Hop WC, Duron JJ, Pailler JL, et al. Foreign material in postoperative adhesions. *Ann Surg* 1996;**223**(3):242–8.
14 Monk BJ, Berman ML, Montz FJ. Adhesions after extensive gynecologic surgery: clinical significance, etiology, and prevention. *Am J Obstet Gynecol* 1994;**170**(5 Pt 1):1396–403.
15 Hull TL, Joyce MR, Geisler DP, Coffey JC. Adhesions after laparoscopic and open ileal pouch-anal anastomosis surgery for ulcerative colitis. *Br J Surg* 2012;**99**(2):270–5.
16 Schäfer M, Krähenbühl L, Büchler MW. Comparison of adhesion formation in open and laparoscopic surgery. *Dig Surg* 1998;**15**(2):148–52.
17 Polymeneas G, Theodosopoulos T, Stamatiadis A, Kourias E. A comparative study of postoperative adhesion formation after laparoscopic vs open cholecystectomy. *Surg Endosc* 2001;**15**(1):41–3.
18 Levrant SG, Bieber EJ, Barnes RB. Anterior abdominal wall adhesions after laparotomy or laparoscopy. *J Am Assoc Gynecol Laparosc* 1997;**4**(3):353–6.
19 Mais V. Peritoneal adhesions after laparoscopic gastrointestinal surgery. *World J Gastroenterol* 2014;**20**(17):4917–25.
20 Bulletti C, Polli V, Negrini V, Giacomucci E, Flamigni C. Adhesion formation after laparoscopic myomectomy. *J Am Assoc Gynecol Laparosc* 1996;**3** (4):533–6.
21 MedexSupply.com. Ethicon Gynecare Interceed Absorbable Adhesion. 2019. [https://www.medexsupply.com/surgical-supplies-prep-supplies-ethicon-gynecare-interceed-absorbable-adhesion-barrier-10-bx-x_pid-54844.html].
22 Ethicon. Ethicon 4350 GYNECARE INTERCEED Absorbable Adhesion Barrier. 2019. [https://www.ethicon.com/na/products/uterine-and-pelvic-surgery/absorbable-adhesion-barriers/gynecare-interceed-absorbable-adhesion-barrier].
23 Al-Jaroudi D, Tulandi T. Adhesion prevention in gynecologic surgery. *Obstet Gynecol Surv* 2004;**59**(5):360–7.
24 DeCherney AH, diZerega GS. Clinical problem of intraperitoneal postsurgical adhesion formation following general surgery and the use of adhesion prevention barriers. *Surg Clin North Am* 1997;**77**(3):671–88.
25 International Adhesions Society. Products Approved by FDA for Adhesion Prevention, Reduction in Pelvice and/or Abdominal Cavities. 2013. [http://www.adhesions.org/products.htm].
26 Ahmad G, Duffy JM, Farquhar C, Vail A, Vandekerckhove P, Watson A, et al. Barrier agents for adhesion prevention after gynaecological surgery. *Cochrane Database Syst Rev* 2008;**2**:CD000475.
27 Ten Broek RPG, Stommel MWJ, Strik C, van Laarhoven C, Keus F, van Goor H. Benefits and harms of adhesion barriers for abdominal surgery: a systematic review and meta-analysis. *Lancet* 2014;**383**(9911):48–59.
28 Diamond MP. Reduction of adhesions after uterine myomectomy by Seprafilm membrane (HAL-F): a blinded, prospective, randomized, multicenter clinical study. Seprafilm Adhesion Study Group. *Fertil Steril* 1996;**66**(6):904–10.
29 Metwally M, Watson A, Lilford R, Vandekerckhove P. Fluid and pharmacological agents for adhesion prevention after gynaecological surgery. *Cochrane Database Syst Rev* 2006;**2**:CD001298.
30 Mais V, Cirronis MG, Peiretti M, Ferrucci G, Cossu E, Melis GB. Efficacy of auto-crosslinked hyaluronan gel for adhesion prevention in laparoscopy and hysteroscopy: a systematic review and meta-analysis of randomized controlled trials. *Eur J Obstet Gynecol Reprod Biol* 2012;**160**(1):1–5.
31 Ahmad G, Mackie FL, Iles DA, O'Flynn H, Dias S, Metwally M, et al. Fluid and pharmacological agents for adhesion prevention after gynaecological surgery. *Cochrane Database Syst Rev* 2014;**7**:CD001298.
32 Patel S, Yadav A. Prevention of adhesion in laparoscopic gynaecological surgery. *Int J Reprod Contracept Obstet Gynecol* 2016;**5**(12):4099–105.
33 ten Broek RP, Kok-Krant N, Verhoeve HR, van Goor H, Bakkum EA. Efficacy of polyethylene glycol adhesion barrier after gynecological laparoscopic surgery: results of a randomized controlled pilot study. *Gynecol Surg* 2012;**9**(1):29–35.
34 Brown CB, Luciano AA, Martin D, Peers E, Scrimgeour A, diZerega GS. Adept (icodextrin 4% solution) reduces adhesions after laparoscopic surgery for adhesiolysis: a double-blind, randomized, controlled study. *Fertil Steril* 2007;**88**(5):1413–26.
35 Dieh A, Yassin A, Pickersgill A. Extravasation of 4% icodextrin solution (Adept) following laparoscopic pelvic surgery. *J Obstet Gynaecol* 2005;**25** (5):489–90.
36 Carpenter TT, Kent A. Ovaries do not float. *Gynecol Surg* 2004;**1**(4):263–4.
37 Reid RL, Hahn PM, Spence JE, Tulandi T, Yuzpe AA, Wiseman DM. A randomized clinical trial of oxidized regenerated cellulose adhesion barrier (Interceed, TC7) alone or in combination with heparin. *Fertil Steril* 1997;**67** (1):23–9.
38 Tulandi T, Closon F, Czuzoj-Shulman N, Abenhaim H. Adhesion barrier use after myomectomy and hysterectomy: rates and immediate postoperative complications. *Obstet Gynecol* 2016;**127**(1):23–8.
39 Wilson MS. Practicalities and costs of adhesions. *Colorectal Dis* 2007;**9** (Suppl 2):60–5.
40 Cheong Y, Sadek K, Watson A, Metwally M, Li TC. Adhesion reduction agents in gynaecological procedures: can NHS afford it? An economic cost efficiency analysis. *J Obstet Gynaecol* 2011;**31**(7):631–5.
41 Haensig M, Mohr FW, Rastan AJ. Bioresorbable adhesion barrier for reducing the severity of postoperative cardiac adhesions: Focus on REPEL-CV (®). *Med Devices (Auckl)* 2011;**4**:17–25.