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**Adhesion prevention agents for gynaecological surgery: an overview of Cochrane reviews**

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**ABSTRACT**

This is the protocol for a review and there is no abstract. The objectives are as follows:

To summarise evidence derived from Cochrane systematic reviews on the clinical safety and effectiveness of solid barriers, gel and liquid agents, and pharmacological agents used as adjuvants to prevent formation of adhesions after gynaecological pelvic surgery.

**BACKGROUND**

Intraperitoneal adhesions are associated with considerable comorbidity and have large financial and public health repercussions. They are the most common complication of gynaecological surgery, forming in 50% to 100% of women (diZerega 1994); secondary effects of adhesions include chronic pelvic pain, dyspareunia, subfertility and bowel obstruction (Broek 2013; SRS 2007). In women with adhesions, subsequent surgery is more difficult, often takes longer and is associated with a higher complication rate (Broek 2013). The significant burden of adhesions has led to the development of several antiadhesion agents, although significant disagreement continues as to which is the most effective. A Cochrane systematic review has been carried out to investigate intraperitoneal prophylactic antiadhesion agents in non-gynaecological surgery (Kumar 2009), but as yet, no unifying review has investigated their role in gynaecological surgery.

**Description of the condition**

Adhesions are fibrin bands that form as the result of aberrant peritoneal healing (Cheong 2001). Normally, peritoneal damage causes an inflammatory response, which activates the coagulation cascade. This leads to formation of a fibrin plug over the damaged mesothelium, which then is broken down to reveal regenerated peritoneum. However, with adhesion formation, fibrinolysis of the fibrin plug is decreased, and consequently, a fibrin matrix develops. Adhesions may be defined as 'de novo,' meaning that they have formed at a location that was previously free from adhesions, or 're-formed,' which indicates that adhesions have recurred post adhesiolysis. In addition to surgery, causes of adhesions include endometriosis, infection (particularly pelvic inflammatory disease) and ischaemia (Diamond 2001). Although the aetiologies are different, the basic pathogenesis of these adhesions is similar.
Description of the interventions

Adhesions can be surgically removed, although because of the high propensity for adhesions to re-form, the clinical effectiveness of adhesiolysis has been controversial (Hammad 2004). Thus the focus of adhesion management is now prevention. Various measures can be taken to prevent adhesions from forming. One of the best recognised measures is careful surgical technique, as tissue trauma and bacterial infection have strong links to the condition. Likewise, more traumatic forms of surgery, such as myomectomy, lead to increased risk of damage. Thus resultant adhesion formation compares with that seen in less invasive procedures such as laparoscopy (Robertson 2010). Adhesiolytic agents may be used to prevent the formation of adhesions primarily through one of two methods: by modifying the processes surrounding adhesion formation, or by creating an inert barrier that allows peritoneal healing to occur.

Adhesion prevention agents fall into two categories: barrier agents and pharmacological agents.

Barrier agents include hydroflotation products, gels and solid agents. Hydroflotation devices include a non-viscous high molecular weight glucose polymer that can be used as an intraperitoneal irrigant and/or instillant. Gel barrier agents commonly include derivatives of hyaluronic acid. Hyaluronic acid is a linear polysaccharide with repeating disaccharide units composed of sodium D-glucuronate and N-acetyl-D-glucosamine; it is a major supportive and protective component of body tissues (Johns 2001). Several solid synthetic barriers with different characteristics are commercially available. These include oxidised regenerated cellulose, expanded polytetrafluoroethylene and fibrin sheet.

Pharmacological agents include steroids, which have been used to prevent adhesions. They can be administered in several ways, including systemically before, during and after surgery, as well as intraperitoneally during surgery, and via hydrotubation postoperatively. Other pharmacological agents used to prevent adhesions include noxytioline, an antibacterial agent; promethazine, an antihistamine; and reteplase, a thrombolytic drug (all of which are absorbed from the peritoneal cavity within seven days and lose. It is absorbed from the peritoneal cavity within seven days and is completely excreted from the body within 28 days (Diamond 1996).

The other commercially available solid barrier is expanded polytetrafluoroethylene (Gore-Tex) surgical membrane (W. L. Gore & Associates, Arizona, USA). It must be sutured in place and is inert and permanent. Other products include Seprafilm (Genzyme Corporation, Cambridge, USA), an adhesion barrier composed of chemically derived sodium hyaluronate and carboxymethylcellulose. It is absorbed from the peritoneal cavity within seven days and is completely excreted from the body within 28 days (Diamond 1996).

Another barrier called the fibrin sheet (TachoComb, Torii Pharmaceutical, Tokyo, Japan) 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. It has been suggested that the fibrin sheet may offer adhesion prevention effects following myomectomy (Mais 1995a; Pellicco 2003). Adverse effects of barrier agents have been reported, including access formation, foreign body reaction and the possibility of actually inducing adhesions rather than preventing them. However, these reactions are thought to be rare and evidence is limited to isolated case reports (Brock 2014; Diamond 2012).

How the intervention might work

Fluid agents such as icodextrin and dextran work by hydroflotation, whereby fluids separate raw opposing surfaces until the healing process has been completed. Fluid agents are believed to remain in the peritoneal cavity for several days, which may be considered a sufficient time, given that adhesions form within eight days of surgery (Diamond 2001; Hosie 2001). Steroids and antihistamines (e.g. promethazine) act as immunomodulating agents and have been used in the belief that they promote fibrinolysis during healing, without hindering the healing process. GnRHa may work by decreasing oestrogen-related growth factors and promoting fibroblasts.

Gel-based barrier agents include polyethylene glycol (PEG), which is a polymer of hyaluronic acid. When two PEG–containing liquids are sprayed simultaneously, they form a cross-linked gel, which prevents denuded tissues from coming in contact with each other. This theoretically prevents the occurrence of adhesions.

With regards to synthetic barriers, oxidised regenerated cellulose was the first tested synthetic mechanical barrier to cover traumatised peritoneum in the pelvis. Interceed is an oxidised regenerated cellulose (Johnson & Johnson, Cincinnati, USA) that can be cut as necessary and is absorbable. It is applied over raw tissue surfaces at the end of surgery after haemostasis has been achieved. It forms a gelatinous coat, which, according to manufacturers, protects against adhesions within eight hours of application. It is broken down into its monosaccharide constituents and is absorbed within two weeks.

Why it is important to do this overview

Adhesions negatively impact women in a variety of ways following pelvic surgery. Symptomatically, adhesions may present with dyspareunia, subfertility and bowel obstruction. Adhesions have also been linked with chronic pelvic pain, although this association remains controversial because the extent of the adhesions does not always correlate with the level of pelvic pain, and reports have been mixed as to whether treatment of adhesions actually improves symptoms (Cheong 2014; Swank 2003). Nevertheless, these consequences can greatly decrease a woman’s well-being and necessitate further surgery. Subsequent surgery in women with adhesions is more difficult, often takes longer and
is associated with a higher complication rate. In 2002 it was estimated that the cost of adhesion-related readmissions in the UK during the first year after lower abdominal surgery was £24.2 million, which increased to £95.2 million in the subsequent nine years (Wilson 2002). The Surgical and Clinical Adhesions Research study (SCAR) found that 5% (n = 245) of readmissions 10 years after open gynaecological surgery were due to adhesions (Lower 2000; Lower 2004). An English study estimated that the National Health Service (NHS) could save £700,000 per year if an antiadhesion agent that reduced adhesions by 25% and cost £110 was used; at worst, its use would be cost-neutral (Cheong 2001).

Considerable disagreement about the effectiveness of adhesion prevention agents can be found in the literature, in part because studies investigating these agents base their results on different endpoints, such as severity of adhesions or the area in which they may form. Indeed many adhesion scoring systems have been developed to help clinicians grade the severity of adhesions and obtain a measure of treatment effect. However, it has been shown that the extent of adhesions does not always correlate with reduction in clinically relevant symptoms. This overview will explore the various endpoints identified in the individual studies and will aim to determine the extent to which surrogate markers are used in the literature.

This overview also seeks to provide an up-to-date and coherent document that will guide clinicians and policy makers regarding the efficacy of solid mechanical barriers, fluid and pharmacological agents, and to clarify which adhesion prevention agents are most effective.

**OBJECTIVES**

To summarise evidence derived from Cochrane systematic reviews on the clinical safety and effectiveness of solid barriers, gel and liquid agents, and pharmacological agents used as adjuvants to prevent formation of adhesions after gynaecological pelvic surgery.

**METHODS**

**Criteria for considering reviews for inclusion**

Only published Cochrane reviews will be considered for inclusion in this overview.  

**Types of participants**

Women in any age group undergoing gynaecological pelvic surgery (laparoscopy or laparotomy).

**Types of interventions**

Solid barrier, liquid and gel agents and pharmacological agents used in gynaecological surgery to prevent adhesions will be considered. Any agent will be compared with any other agent or with no treatment, if available. These include the following.

1. **Liquid and gel agents.**
   - i) Oxiplex versus no treatment.
   - ii) Spraygel versus no Spraygel.
   - iii) Adept versus Ringer’s lactate.
   - v) InterGel versus Ringer’s lactate.
   - vi) Above agents versus each other.
   - vii) Other agents.

2. **Solid agents.**
   - i) Interceed versus no Interceed.
   - ii) Gore-Tex versus no Gore-Tex.
   - iii) Gore-Tex versus Interceed.
   - iv) Seprafilm versus no Seprafilm.
   - v) Above agents versus each other.
   - vi) Other agents.

3. **Pharmacological agents.**

**Types of outcome measures**

1. **Primary outcomes.**
   - i) Pelvic pain (new pain/change in severity of pain/improvement in pain).
   - iii) Live birth rate.
   - iv) Quality of life measures in included reviews (QoL).

2. **Secondary outcomes**
   - i) Adverse outcomes-local and systemic-including need for removal of barrier agents.
   - ii) Change in adhesion score.
     - a) Presence or absence of adhesions at second-look laparoscopy (SLL) (bimodal outcome).
     - b) Adhesion score.
     Adhesion score at SLL (non-parametric continuous data).
     Improvement or deterioration in adhesion score (for studies reviewing adhesion reformation prevention strategies) (bimodal outcome).

**Search methods for identification of reviews**

The Cochrane Database of Systematic Reviews and the Menstrual Disorders and Subfertility Group review database will be searched using the keyword ‘adhesion.’ The term will be restricted to title, abstract or keywords. The Cochrane information management system (Archie) will also be searched for any titles or protocols of reviews in progress. Any relevant protocols that are found will be considered for incorporation into the review.

**Data collection and analysis**
Selection of reviews
Reviews addressing the use of antiadhesion agents for prevention in gynaecological surgery will be identified by one review author and confirmed by a second review author. Disagreement will be resolved by consensus or by discussion with a third review author.

Data extraction and management
Two review authors (AH, LB) will independently extract information from the papers. Data will be transferred onto an Excel spreadsheet to allow review authors to combine and reformat information in data discussions and in figures. Disagreements will be resolved by a third review author (GA or AW). When data are missing, the original study authors will be contacted for assistance.

Data will be managed within a Microsoft Access database before input into RevMan. The statistical package RevMan 5.2, provided by The Cochrane Collaboration, will be used to analyse and synthesise data. Evidence will be sought that the review authors made attempts to retrieve missing data from the original trial authors. If this is not documented, we shall aim to contact trial authors directly to retrieve the information.

Assessment of methodological quality of included reviews

Quality of included reviews

Acknowledgements
Currently, two Cochrane reviews (Ahmad 2008; Ahmad 2014) have assessed the effectiveness of adhesion prevention agents. Several of the authors of the present overview contributed to both of these reviews. Ahmad 2014 evaluated fluid and pharmacological agents, and Ahmad 2008 analysed mechanical barrier agents. The latter review is in the process of being updated.

We acknowledge the contributions of Dr Helena O’Flynn to early drafts of this protocol.

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Ahmad 2008

Ahmad 2014

Broek 2013

Broek 2014

Cheong 2001

Cheong 2014
Cheong Y, Reading I, Bailey S, Sadek K, Ledger W, Li T. Should women with chronic pelvic pain have adhesiolysis?. *BMC Women’s Health* 2014;14:36.

Diamond 1996
Diamond 2001

Diamond 2012

diZerega 1994

Hammoud 2004

Hosie 2001

Johns 2001

Kumar 2009

Lower 2000

Mais 1995a

Pellicno 2003

Robertson 2010

SRS 2007

Swank 2003

Wilson 2002

* Indicates the major publication for the study

CONTRIBUTIONS OF AUTHORS

GA conceived the idea, helped draft the protocol, supervised AH
SD helped with planning the data analysis
AH drafted the protocol
LB assisted in drafting the protocol
AW helped in developing the protocol idea and supervised the co-authors.
DECLARATIONS OF INTEREST
None.

SOURCES OF SUPPORT

Internal sources
• None, Other.

External sources
• None, Other.

NOTES
None