Anti-adhesion therapy following operative hysteroscopy for treating female subfertility (Protocol)

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Anti-adhesion therapy following operative hysteroscopy for treating female subfertility

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ABSTRACT

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

To assess the effectiveness of anti-adhesion therapy versus placebo, no therapy or an alternative anti-adhesion therapy following operative hysteroscopy for the treatment of female subfertility.

BACKGROUND

Description of the condition

Intrauterine adhesions (IUAs) are fibrous strings at opposing walls of the uterus. The spectrum of severity of IUAs ranges from minimal to the complete obliteration of the uterine cavity. Any trauma to the endometrium (the inner layer of the uterus) may lead to the formation of de novo IUAs; and nearly 90% of all cases of IUAs are associated with postpartum or postabortion dilatation and curettage (Nappi 2007). The etiological role of infection in the formation of IUAs is, with the exception of genital tuberculosis, controversial (Deans 2010). IUA formation is the major long-term complication of hysteroscopic surgery in women of reproductive age. A randomized controlled trial reports the incidence of postsurgical IUAs at second look hysteroscopy as 3.6% after polypectomy, 6.7% after resection of uterine septa, 31.3% after removal of a solitary myoma and 45.5% after resection of multiple myomas (Taskin 2000). The mechanisms of tissue repair in the human endometrium are poorly understood (Revaux 2008) despite several hypotheses on the origin of cells for endometrial regeneration (Okulicz 2002). Endometrial stem or progenitor cells, present in the human and rodents, may have an important function in endometrial regeneration in normal menstrual cycles and after delivery; this holds promise for new treatments for subfertility associated with IUAs or Asherman’s syndrome (Deane 2013). The duration of the endometrial wound healing differs according to the type of pathology as concluded by Yang and co-workers in a prospective cohort study of 163 women undergoing operative hysteroscopy (Yang 2013); the authors reported that the time needed
for a complete recovery of the endometrium ranges from one to three months following the hysteroscopic removal of endometrial polyps and submucous fibroids respectively. IUAs are associated with a poor reproductive outcome. Firstly this is due to infertility with a prevalence as high as 43% (922 of 2151 women) according to a large review of observational studies (Schenker 1982). Secondly, the poor outcome is due to the clinical problem of recurrent miscarriage, ranging from 5% to 39% in women with IUAs according to a review of observational studies (Kodaman 2007). Thirdly, it is due to major and at times devastating obstetric complications, for example placenta accreta or increta and higher risks for preterm delivery, uterine rupture and peripartum hysterectomy as the endpoint of the successful hysteroscopic treatment of severe IUAs (Deans 2010).

**Description of the intervention**

Several observational studies have suggested different anti-adhesion strategies for preventing de novo adhesion formation following operative hysteroscopy.

**Intrauterine contraceptive device or Foley catheter balloon**

An intrauterine contraceptive device (IUD) may provide a physical barrier between the uterine walls, separating the endometrial layers after lysis of IUAs. Its insertion as an adjunctive therapy has been recommended in at least 13 observational studies (Deans 2010). The use of a Foley catheter balloon has been reported as an alternative, for similar purposes, in eight observational studies (Deans 2010).

**Hormone therapy**

In 1964, Wood and Pena suggested the use of estrogen therapy to stimulate the regeneration of the endometrium after the surgical treatment of IUAs (Wood 1964).

**Barrier gels**

Hyaluronic acid or hyaluronan (HA), is a water soluble polysaccharide. It consists of multiple disaccharide units of glucuronic acid and N-acetylglucosamine bound together by a β1-3-type glucoside bond. Solutions of HA have visco-elastic properties that have led to interest in developing applications of HA in surgical procedures, for example in ocular surgery and prevention of postsurgical adhesions. However, HA may not be the ideal substance for all procedures due to its limited residence time when applied to a surgical site. It quickly enters the systemic circulation and is then cleared rapidly by catabolic pathways. Attempts to use hyaluronan for preventing postsurgical adhesions have therefore been met with variable success. Chemically modified derivatives of HA have been developed to circumvent the disadvantages of HA. One such derivative is auto-crosslinked polysaccharide (ACP). It is formed by crosslinking hyaluronan via direct formation of covalent ester bonds between hydroxyl and carboxyl groups of the hyaluronan molecule. ACP can be prepared with various degrees of crosslinking, which allows tailoring of the viscosity properties of ACP gels (Renier 2005). Carboxymethylcellulose (CMC) is a high molecular-weight polysaccharide that has a viscosity greater than dextran 70. CMC can be used for adhesion prevention as a membrane barrier or a gel as a mixture of chemically derivative sodium hyaluronate and carboxymethylcellulose gel (HA-CMC) (Leach 1998).

**Human amnion membrane grafting**

Over the last three decades, the surgical community has become more aware of the increasing potential of human amnion membrane (HAM) as an adjunctive anti-adhesion intervention. The use of whole human fetal membranes or amnion alone in surgery has primarily developed to aid the repair of surface epithelial defects in the skin, eye, abdominal wall and peritoneum. HAM grafting has not been very popular in the field of obstetrics and gynaecology; its clinical use is limited to as a graft in forming an artificial vagina or as a barrier to prevent postoperative intra-abdominal adhesion formation, or finally as a biological dressing following radical vulvectomies and groin dissections (Amer 2006).

**How the intervention might work**

The hypothetical underlying mechanisms of infertility associated with IUAs are obstruction of sperm transport into the cervix, impaired embryo migration within the uterine cavity or failure of embryo implantation due to endometrial insufficiency (Deans 2010). The ideal anti-adhesion adjunctive therapy following operative hysteroscopy would be the application of a biologically active mechanical separator that achieves the suppression of intrauterine adhesion formation and promotes the healing of the endometrium. The bulk of evidence on how the different interventions might work is derived from animal studies, largely in rodents and not in validated animal models for the study of human reproduction (D’Hooghe 2009), or observational studies.

**Intrauterine contraceptive device (IUD) or Foley catheter balloon**

The use of an IUD (13 observational studies) or a Foley catheter balloon (eight observational studies) (Deans 2010) is often recommended following the hysteroscopic treatment of IUAs or septoplasty, to act as a physical barrier separating the opposing walls of the uterine cavity. The type of IUD may be important; copper-containing IUDs provoke an inflammatory reaction, probably with detrimental effects, whereas T-shaped IUDs might have
too small a surface area to be truly effective in providing an efficient physical barrier. The loop IUD (for example Lippes loop) is generally considered the IUD of choice when treating IUAs; it is, however, no longer available in many countries (Kodaman 2007). One clinical controlled trial (Orhue 2003) compared the use of a Foley catheter balloon for 10 days (N = 59) versus the insertion of an IUD during a three month period (N = 51); the fertility rates were poor in both the IUD group (20/59 or 34%) and the Foley catheter group (14/51 or 28%).

Hormone therapy

Many studies recommend the use of a cyclical estrogen and progestogen treatment regimen following the hysteroscopic treatment of IUAs to promote the regeneration of the endometrium (Deans 2010). Various regimens have been proposed consisting of estrogen (for example a typical daily dose of 2.5 mg of conjugated equine estrogen twice daily for 30 days) with or without a progestin (for example 10 mg medroxyprogesterone acetate for 10 days) (Kodaman 2007). No comparative studies have been performed on dosage, administration or combination of hormones (Deans 2010). In a randomized controlled trial (Farhi 1993) 60 women undergoing dilation and curettage during the first trimester of pregnancy were allocated to receive estrogen and progestin or no treatment. Women in the intervention group had a significantly thicker endometrium (8.4 versus 6.7 mm, P = 0.02) compared with the control group. The authors concluded that postoperative hormone treatment may be beneficial for intrauterine adhesion prevention following surgical trauma to the uterine cavity. Nevertheless, no data were available on pregnancy outcome or intrauterine adhesion recurrence (Farhi 1993). A systematic review of observational studies concluded that hormonal therapy, particularly estrogen therapy, may be beneficial to women with IUAs but as an adjunctive therapy combined with other anti-adhesion strategies (Johary 2013).

Barrier gels

The use of the biodegradable gel surgical barriers is based on the principle of keeping the adjacent wound surfaces mechanically separate (Renier 2005). Several preclinical studies in various animal models have demonstrated the effectiveness of both ACP (Belluco 2001; Binda 2007; Binda 2009; Binda 2010; De Iaco 1998; Koçak 1999; Shamiyeh 2007; Wallwiener 2006) and HA-CMC gels (Leach 1998; Schonman 2008) or HA-CMC membranes (Kelecki 2004; Rajab 2010) for preventing postsurgical adhesions. Other preclinical studies in animal models suggest that HA gel remains in situ for more than five to six days (Laurent 1992; Nimrod 1992). Similarly, animal studies demonstrate the persistence of HA-CMC for about seven days after its application (Diamond 1988). The exact mechanisms by which ACP and HA-CMC are able to reduce adhesion reformation are not well known but may be related to 'hydrofloation' or 'siliconizing' effects. One French clinical controlled trial (N = 54 women) compared the application of ACP gel (N = 30) versus no gel at the end of an operative hysteroscopic procedure for treating myomas, polyps, uterine septa or IUAs; there were no statistically significant differences for the rate of adhesion formation between comparison groups, nor for the mean adhesion scores or the severity of the adhesions (Ducarme 2006). There were no data on the reproductive outcome.

Human amnion membrane grafting

The preclinical data on the effectiveness of HAM grafting in different animal models present conflicting results. One trial (Szabo 2002) demonstrates a beneficial effect in preventing de novo adhesions whereas according to two other animal studies (Arora 1994; Badawy 1989) HAM grafting fails to prevent de novo adhesion formation. One observational study reports data on the use of a fresh amnion graft over an inflated Foley catheter to prevent recurrence of intrauterine adhesions after hysteroscopic lysis in 25 women with moderate to severe Asherman syndrome. Minimal adhesion reformation was demonstrated in 48% of the study participants with severe adhesions. The authors conclude that HAM grafting might be promising as an adjunctive therapy following hysteroscopic adhesiolysis; it acts as a biologically active mechanical barrier suppressing adhesion formation and promoting endometrial healing (Amer 2006). A fresh HAM graft preserves its viability for 21 days following its application in the pelvic cavity (Treford Sauder 1977). In addition to being an anatomical barrier HAM may promote the regeneration of epithelium by acting as a basement membrane substrate; HAM may also facilitate the migration of epithelial cells, reinforce the adhesion of the basal epithelium, promote epithelial cell differentiation (Meller 1999) and prevent cellular apoptosis (Hori 2006). Human amnion epithelial cells produce factors or create a microenvironment for effective tissue repair and endometrial regeneration, possibly by stimulating endogenous stem cells (Padykula 1991).

Why it is important to do this review

At present it is not clear whether the use of anti-adhesion therapies after operative hysteroscopy might be beneficial for the outcomes of pregnancy or live birth. Answering this question is the main objective of this Cochrane review. Moreover, little is known about the relative contribution of different anti-adhesion strategies in increasing reproductive benefit in women wishing to conceive following operative hysteroscopy; this head to head comparison of the alternative anti-adhesion interventions is a secondary objective of the present research. Adhesions may cause infertility, abdominal pain, or bowel obstruction. The health burden associated with these three clinical problems is substantial (DeCherney 1997; diZerega 1994; Renier
The total cost of adhesion-related morbidity in the US Health Care system exceeds $1 billion annually (Baakdah 2005). One trial in the domain of gynaecologic oncology (Bristow 2007) evaluated the cost-effectiveness of using a HA-CMC anti-adhesion barrier compared to routine care, in which no adhesion prevention measures were taken, through a decision analysis model in the setting of women undergoing radical hysterectomy and pelvic lymphadenectomy for stage IB cervical cancer. The authors concluded that given a conservative set of clinical and economic assumptions, an adhesion prevention strategy utilizing a HA-CMC barrier in women undergoing radical hysterectomy for Stage IB cervical cancer might be cost-effective from both the perspective of society as a whole and that of a third party payer. To the best of our knowledge there are no cost-effectiveness studies on adhesion prevention after operative hysteroscopy in an infertile population; the evidence retrieved from the present research could be the basis for further economical studies of different anti-adhesion treatments. This is another secondary objective of the present review. Infertility, the inability to conceive after a defined period of unprotected intercourse, is an often neglected aspect of reproductive health worldwide. The official development of assistance for reproductive health care and family planning remains low worldwide despite an increasing absolute number of couples affected by infertility, from 42.0 million in 1990 to 48.5 million in 2010 (Mascarenhas 2012). Therefore the World Health Organization (WHO) has recognized reproductive health as a priority global health area; the target for the United Nations Millennium Development Goal 5B is to provide universal access to reproductive health by 2015 (http://www.un.org/millenniumgoals/maternal.shtml).

OBJECTIVES

To assess the effectiveness of anti-adhesion therapy versus placebo, no therapy or an alternative anti-adhesion therapy following operative hysteroscopy for the treatment of female subfertility.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished parallel group randomised controlled trials (RCTs) will be eligible for inclusion. We will exclude non-randomised studies (for example studies with evidence of inadequate sequence generation such as alternate days, patient numbers) as they are associated with a high risk of bias. We will include crossover trials if individually randomized women are the unit of analysis; only data from the first phase will be included in the meta-analyses as the crossover trial is not a valid study design in the context of subfertility.

Types of participants

Women of reproductive age undergoing operative hysteroscopy for subfertility associated with suspected or unsuspected intrauterine pathology before spontaneous conception or any subfertility treatment. Studies excluding women wishing to conceive will not be eligible.

Types of interventions

We will include the following randomised comparisons:
- anti-adhesion therapy versus placebo or no active anti-adhesion therapy following operative hysteroscopy;
- anti-adhesion therapy A versus anti-adhesion therapy B following operative hysteroscopy.

Types of outcome measures

Primary outcomes

1. Effectiveness: live birth, defined as delivery of at least one live fetus after 20 weeks of gestation that resulted in the birth of at least one live baby; we will count the delivery of singleton, twin or multiple pregnancies as one live birth.

Secondary outcomes

3. Effectiveness: clinical pregnancy, defined as a pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy; this includes ectopic pregnancy. We will count multiple gestational sacs as one clinical pregnancy.
4. Adverse event: miscarriage, mean adhesion scores and severity of adhesions at second look hysteroscopy. A miscarriage is the spontaneous loss of a clinical pregnancy that occurs before 20 completed weeks of gestation (18 weeks postfertilization) or, if gestational age is unknown, the loss of an embryo or fetus of less than 400 g.

We will avoid excluding studies on the basis of their reported outcome measures. Eligible studies that could have measured the outcomes of interest will be reviewed; we will report any lack of data for the key outcomes in the final review.

We aim to follow the International Committee for Monitoring Assisted Reproductive Technology (ICMART) terminology for the key reproductive outcomes (live birth, pregnancy and miscarriage) as much as possible (Zegers-Hochschild 2009); we will contact...
the primary study authors for clarification in the case of unclear definitions. We will report any discrepancies in the final review. There are at present seven reported classification systems for scoring the extent or severity of intrauterine adhesions. None of these systems have been validated or universally accepted (Deans 2010). We will therefore avoid pooling data from studies using different scoring systems; we will seek clarification from the primary study authors if necessary.

According to a prospective cohort study the duration of the endometrial wound healing may be different according to the type of pathology; the authors concluded that the recovery of the endometrium may vary from one month (after hysteroscopic removal of polyps) to three months (following hysteroscopic myomectomy) (Yang 2013). We will only pool studies when the assessment of intrauterine adhesions by second loop hysteroscopy was done between four and 12 weeks following operative hysteroscopy. We will analyse data for the adverse events separately and not as one composite measure.

### Search methods for identification of studies

We will search for all published and unpublished RCTs of anti-adhesion therapies following operative hysteroscopy in subfertile women, without language restriction and in consultation with the Menstrual Disorders and Subfertility Group (MDSG) Trials Search Co-ordinator.

#### Electronic searches

We will search the following electronic databases, trial registers and websites using the search strategies in the appropriate appendices: the Cochrane Central Register of Controlled Trials (CENTRAL) (Appendix 1), the Menstrual Disorders and Subfertility Group (MDSG) Specialised Register (Appendix 2), MEDLINE using Ovid (Appendix 3) and EMBASE using EMBASE.com (Appendix 4) (from inception to the present).

The search strategy will combine both index and free-text terms. Our MEDLINE search will include the Cochrane highly sensitive search strategy for identifying randomised trials using the format which appears in the Cochrane Handbook for Systematic Reviews of Interventions (http://www.cochrane.org/training/cochrane-handbook).

Our EMBASE search will include the trial filter developed by the Scottish Intercollegiate Guidelines Network (www.sign.ac.uk/methodology/filters.html#random).

Other electronic sources of trials will include:

- Cochrane Database of Systematic Reviews (CDSR) (from inception until the present);
- Database of Abstracts of Reviews of Effectiveness (DARE) and the Health Technology Assessment Database (HTA Database) through the Centre for Reviews and Dissemination (http://www.crd.york.ac.uk) (from inception until the present);
- National Guideline Clearinghouse (http://www.guideline.gov/) for evidence-based guidelines (from inception until the present);
- BIOSIS previews through ISI Web of Knowledge (http://iswbofknowledge.com) (Appendix 5) and CINAHL (http://www.ebscohost.com/biomedical-libraries/the-cinahl-database) (Appendix 6) through EBSCOHost, available at the Biomedical Library Gasthuisberg of the Catholic University of Leuven (from inception until the present);
- trial registers for ongoing and registered trials ‘Current Controlled Trials’ (http://www.controlled-trials.com), ‘ClinicalTrials.gov’ provided by the US National Institutes of Health (http://clinicaltrials.gov/ct2/home) and the WHO International Clinical Trials Registry Platform search portal (http://apps.who.int/trialsearch/) (from inception until the present);
- the citation indexes Science Citation Index through Web of Science (http://scientific.thomson.com/products/sci/) (Appendix 5) - SCI-EXPANDED and Conference Proceedings Citation Index - Science (CPCI-S) (from inception until the present);
- conference abstracts and proceedings on the Web of Knowledge (http://wokinfo.com/) (Appendix 5) applying ‘SCI-EXPANDED’ and ‘CPCI-S’ (from inception until the present);
- LILACS database, which is a source of trials from the Spanish and Portuguese speaking world (http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&cform=F) (from inception till the present);
- European grey literature through the Open Grey database (http://www.opengrey.eu/subjects/) (from inception until the present);
- general search engines Turning Research into Practice (TRIP) database (http://www.tripdatabase.com/), Google Scholar (http://scholar.google.be/advanced_scholar_search) and Scirus (http://www.scirus.com) (from inception until the present).

#### Searching other resources

Two review authors (JB and JK) will handsearch reference lists of articles retrieved by the search and contact experts in the field to obtain additional data. We will contact the first or corresponding authors of included studies to ascertain if they are aware of any ongoing or unpublished trials. We will also handsearch relevant journals and conference abstracts that are not covered in the MDSG Specialised Register, in liaison with the Trials Search Coordinator. The search process will be reported in a PRISMA flow diagram in the review.

### Data collection and analysis

Anti-adhesion therapy following operative hysteroscopy for treating female subfertility (Protocol)

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Selection of studies

After an initial screen of titles and abstracts retrieved by the search, conducted by JB, the full texts of all potentially eligible studies will be retrieved. Two review authors (FB and TD) will independently examine these full text articles for compliance with the inclusion criteria and select studies eligible for inclusion in the review. We will correspond with study investigators, as required, to clarify study eligibility. Disagreements as to study eligibility will be resolved by discussion or by a third review author (BWM). We will classify the study as ‘awaiting classification’ if disagreements between review authors cannot be resolved and we will report the disagreement in the final review.

Data extraction and management

Two review authors, one a methodologist (JB) and one a topic area specialist (SW), will independently extract data from eligible studies using a data extraction form designed and pilot-tested by the authors. Any disagreements will be resolved by discussion or by a third review author. The data extracted will include study characteristics and outcome data (Appendix 7). Where studies have multiple publications, the main trial report will be used as the reference and additional details will be derived from secondary papers. We will correspond with study investigators for further data on methods and results, as required. We will include studies irrespective of whether outcomes are reported in a ‘usable’ way. In multi-arm studies, data from arms that do not meet the eligibility criteria will be excluded.

Assessment of risk of bias in included studies

Two review authors (JB and SW) will independently assess the included studies for risk of bias using the Cochrane risk of bias tool (http://www.cochrane.org/training/cochrane-handbook). The following seven items will be assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other potential sources of bias. We will resolve disagreements by discussion or by a third review author. We will describe all judgements fully and present the conclusions in the ‘Risk of bias’ table, which will be incorporated into the interpretation of review findings by means of sensitivity analyses.

Selective reporting is a type of reporting bias that affects the internal validity of an individual study (see Table 10.1A in the Cochrane Handbook for Systematic Reviews of Interventions) (http://www.cochrane.org/training/cochrane-handbook). It refers to the selective reporting of some outcomes (for example positive outcomes) and the failure to report others (for example adverse events). We will take care to search for within-trial selective reporting, such as trials failing to report obvious outcomes, or reporting them in insufficient detail to allow inclusion. We will seek published protocols and compare the outcomes between the protocol and the final published study. Where identified studies fail to report the primary outcome of live birth, but do report interim outcomes such as pregnancy, we will undertake informal assessment as to whether the interim values (for example pregnancy rates) are similar to those reported in studies that also report live birth. If there are outcomes defined in the protocol or the study report with insufficient data to allow inclusion, the review will indicate this lack of data and suggest that further clinical trials need to be conducted to clarify these knowledge gaps.

Measures of treatment effect

For dichotomous data (for example live birth or clinical pregnancy rates), we will use the numbers of events in the control and intervention groups of each study to calculate Mantel-Haenszel odds ratios (ORs). We will treat ordinal data (for example adhesion scores) as continuous data. For ordinal data (for example adhesion scores), if all studies report exactly the same outcomes we will calculate mean differences (MDs) between treatment groups. If similar outcomes are reported on different scoring scales we will not calculate the standardised mean difference (SMD) since the seven different adhesion score classifications have not been validated. We will reverse the direction of effect of individual studies, if required, to ensure consistency across trials. We will present 95% confidence intervals (CIs) for all outcomes. We will make contact with the corresponding or first authors of all included trials that report data in a form that is not suitable for meta-analysis, for example time-to-pregnancy data (TTP). We will report the data of those reports that fail to present additional data that could be analysed under ‘other data’. We will not include TTP data in any meta-analysis. Where the data to calculate ORs or MDs are not available, we will utilise the most detailed numerical data available that may facilitate similar analyses of included studies (for example test statistics, P values). We will compare the magnitude and direction of effect reported by studies with how they are presented in the review, taking account of legitimate differences.

Unit of analysis issues

The primary analysis will be per woman randomised; per pregnancy data will be included for some outcomes (for example miscarriage). If studies report only per cycle data, we will contact the primary study authors and request per woman data. If these are not available, the per cycle data will be briefly summarised in an additional table and will not be included in a meta-analysis. Multiple live births (for example twins or triplets) will be counted as one live birth event. Only first-phase data from crossover trials will be included.

Dealing with missing data

We will analyse the data on an intention-to-treat basis as far as possible; if needed, attempts will be made to obtain missing data
from the original researchers. Where these are unobtainable, imputation of individual values will be undertaken for the beneficial primary outcome (live birth) only; we will assume that live births would not have occurred in women without a reported outcome. For all other outcomes we will only analyse the available data. Any imputation undertaken for missing data for the primary outcome will be subjected to sensitivity analysis (See: Sensitivity analysis). If studies report sufficient detail to calculate mean differences but do not provide information on associated standard deviations (SDs), the outcome will be assumed to have an SD equal to the highest SD from other studies within the same analysis.

Assessment of heterogeneity
We will consider whether the clinical and methodological characteristics of the included studies are sufficiently similar for meta-analysis to provide a clinically meaningful summary. We will carry out a formal assessment of statistical heterogeneity by using the I² statistic combined with the Q-statistic. Cochran’s Q test, a form of Chi² statistic, is the classical measure to test for significant heterogeneity. Cochran’s Q test is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies. The Q-statistic follows the Chi² distribution with k-1 degrees of freedom, where k is the number of studies. Q > k-1 suggests statistical heterogeneity. A low P value for Cochran’s Q test means significant heterogeneous results among different studies; usually a P value of 0.10 is used as the cut-off. The Q-statistic has low power as a comprehensive test of heterogeneity, especially when the number of studies is small. The Q-statistic informs us about the presence or absence of heterogeneity; it does not report on the extent of such heterogeneity. The I² statistic describes the percentage of variation across studies that is due to significant heterogeneity rather than random chance. It measures the extent of heterogeneity. An I² value greater than 50% will be taken to indicate substantial heterogeneity (Higgins 2003). We will explore possible explanations for the heterogeneity if substantial heterogeneity is detected.

Assessment of reporting biases
Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of the results. Some types of reporting bias (for example publication bias, multiple publication bias, language bias) reduce the likelihood that all studies eligible for a review will be retrieved. If all eligible studies are not retrieved, the review may be biased. In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we will aim to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If there are 10 or more studies in an analysis, we will use a funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis
One review author (JB) will enter the data and carry out the statistical analysis of the data in Review Manager 5. If the studies are sufficiently similar and substantial statistical heterogeneity can be confidently ruled out, we will combine the data from the primary studies in a meta-analysis with Review Manager 5; we will use summary Mantel-Haenszel (M-H) ORs and a random-effects model (REM) for the following comparisons:

- anti-adhesion therapy versus placebo or no active anti-adhesion therapy following operative hysterectomy;
- anti-adhesion therapy A versus anti-adhesion therapy B following operative hysterectomy.

The outcomes ‘live birth’ and ‘clinical pregnancy’ are considered positive outcomes of effectiveness and as a consequence higher numbers will be considered as a benefit. The outcomes ‘incidence of de novo adhesion formation’, ‘miscarriage’, ‘mean adhesion scores’ and ‘severity of adhesions’ at second look hysterectomy are negative effects and higher numbers will be considered harmful. An increase in the odds of a particular outcome, which may be beneficial (for example live birth) or detrimental (for example de novo adhesions), will be displayed graphically in the meta-analyses to the right of the centre-line and a decrease in the odds of an outcome to the left of the centre-line.

We will aim to define analyses that are comprehensive and mutually exclusive so that all eligible study results can be slotted into one stratum only in each comparison, and so that trials within the same stratum can sensibly be pooled. Stratification is not a requirement but allows consideration of effects within each stratum as well as, or instead of, an overall estimate for the comparison. The use of the REM instead of a fixed-effect analysis model (FEM) is justified by the fact that the results of a similar surgical treatment may be different across studies; despite rigorous standardisation, there might inevitably be differences in surgical skill among the different surgeons involved in the trials. If no RCTs are retrieved for some comparisons, the review will indicate their absence thus identifying knowledge gaps which need further research. We will undertake a narrative overview if meta-analysis is not appropriate.

Subgroup analysis and investigation of heterogeneity
Where enough data are available, we will conduct subgroup analyses to determine the separate evidence within the following subgroups:

- studies that report both live birth and clinical pregnancy in order to assess any overestimation of the treatment effect and reporting bias;
• according to the type, extent or severity of the uterine abnormality treated.

We will report the interpretation of any subgroup analysis conservatively, even if enough data were available; subgroup analysis is by its nature an observational study that can be helpful in generating or exploring hypotheses. Moreover, the interpretation of the statistical analysis for subgroups is not without problems.

**Sensitivity analysis**

We will conduct sensitivity analyses for the primary outcomes to determine whether the conclusions are robust to arbitrary decisions made regarding the eligibility and analysis of the studies. These analyses will include consideration of whether the review conclusions would have differed if:

- eligibility were restricted to studies without high risk of bias versus all studies;
- a fixed-effect (FEM) rather than a random-effects model (REM) had been adopted;
- alternative imputation strategies had been implemented;
- the summary effect measure was relative risk rather than OR.

**Overall quality of the body of evidence: summary of findings table**

We will generate a ‘Summary of findings’ table for the primary outcomes live birth and incidence of de novo adhesion formation at second look hysteroscopy using GRADEPRO software (version 3.2.2.20090501) (http://ims.cochrane.org/gradepro). This table will evaluate the overall quality of the body of evidence for these two key outcomes using the GRADE criteria (study limitations (that is risk of bias), consistency of effect, imprecision, indirectness and publication bias). Judgements about evidence quality (high, moderate or low) will be justified, documented and incorporated into reporting of results for each outcome.

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Kodaman 2007

Koçak 1999

Laurent 1992

Leach 1998

Mascarenhas 2012
Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in anti-adhesion therapy following operative hysteroscopy for treating female subfertility (Protocol)
Anti-adhesion therapy following operative hysteroscopy for treating female subfertility (Protocol)

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Meller 1999

Nappi 2007

Nimrod 1992

Okulicz 1999

Orhue 2003

Padykula 1991

Rajab 2010

Renier 2005

Revaux 2008

Schenker 1982

Schonman 2008

Shamiyeh 2007

Szabo 2002

Taskin 2000

Trelford Sauder 1977

Wallwiener 2006

Wood 1964

Yang 2013

Zegers-Hochschild 2009
Appendix 1. CENTRAL search strategy

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <June 2013>

Search Strategy:

1 exp Hysteroscopy/
2 Hysteroscop$.
tw.
3 uteroscop$.tw.
4 endoscop$ uter$.tw.
5 or/1-4
6 synchyiolysis.tw.
7 Anti-adhesion$.
tw.
8 exp Tissue Adhesions/
9 Adhesio$.
tw.
10 sepracoat.tw.
11 icodextrin.tw.
12 hydrogel.tw.
13 hydrotubation.tw.
14 exp Hyaluronic Acid/
15 hyaluronic acid.tw.
16 intergel.tw.
17 Barrier Membrane$.
tw.
18 hyaluronan.tw.
19 hyaluronidase.tw.
20 promethazine.tw.
21 dextran.tw.
22 adhesion barrier$.
tw.
23 amnion grafi$.
tw.
24 antibiotic$.
tw.
25 Estrogen$.
tw.
26 oestrogen$.
tw.
27 exp Intrauterine Devices/
28 (intrauterine adj2 device$).tw.
29 Ringer Lactate.tw.
30 Oxidized regenerated cellulose.tw.
31 Interceed$.
tw.
32 Seprafile$.
tw.
33 polytetrafluoroethylene.tw.
34 Gore-tex$.
tw.
35 spraygel$.
tw.
36 Crystalloid$.
tw.
37 Adept$.
tw.
38 ACP gel$.
tw.
39 Hyalobarrier gel$.
tw.
Appendix 2. MDSG Specialised Register search strategy

Keywords CONTAINS “hysteroscopy” or “hysteroscopy pain” or “hysteroscopy pain -surgical” or “hysteroscopy, techniques” or “hysteroscope” or “office hysteroscopy” or “operative hysteroscopy” or Title CONTAINS “hysteroscopy” or “hysteroscopy pain” or “hysteroscopy pain -surgical” or “hysteroscopy, techniques” or “hysteroscope” or “office hysteroscopy” or “operative hysteroscopy” AND

Keywords CONTAINS “adhesiolysis” or “adhesion” or “adhesions” or “adhesions outcome” or “adhesion prevention” or “adhesion formation” or “pelvic adhesions” or “Sepracoat” or “icodextrin” or “hydrogel” or “hydrotubation” or “Sepraﬁlm” or “intergel” or “Barrier Membrane” or “hyaluronan” or “hyaluronic acid” or “hyaluronidase” or “Promethazine” or “dextran” or “SprayGel” or “adhesion barrier” or “adhesion barriers” or “post-operative adhesions” or “gynaecologic surgical procedure” or “pelvic adhesions” or “amnion graft” or “antibiotics” or “Estrogen” or “Estrogen” or “oestrogen” or “intrauterine device” or “Intrauterine Devices, Medicated” or “Intrauterine Releasing Devices” or Title CONTAINS “adhesiolysis” or “adhesion” or “adhesions” or “adhesions outcome” or “adhesion prevention” or “adhesion formation” or “pelvic adhesions” or “Sepracoat” or “icodextrin” or “hydrogel” or “hydrotubation” or “Sepraﬁlm” or “intergel” or “Barrier Membrane” or “hyaluronan”

Last update 09/07/2013

Appendix 3. MEDLINE search strategy

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 exp Hysteroscopy/
2 Hysteroscop$.tw.
3 uteroscop$.tw.
4 endoscop$.uter$.tw.
5 or/1-4
6 synechiolysis.tw.
7 Anti-adhesion$.tw.
8 exp Tissue Adhesions/
9 Adhesio$.tw.
10 sepracoat.tw.
11 icodextrin.tw.
12 hydrogel.tw.
13 hydrotubation.tw.
14 exp Hyaluronic Acid/
15 hyaluronic acid.tw.
16 intergel.tw.
17 Barrier Membrane$.tw.
18 hyaluronan.tw.
19 hyaluronidase.tw.
20 Promethazine.tw.
21 dextran.tw.
22 adhesion barrier$.tw.
23 amnion graft$.tw.
24 antibiotic$.tw.
25 Estrogen$.tw.
Appendix 4. EMBASE search strategy

Database: Embase <1980 to 2013 July 09>

Search Strategy:

1 exp Hysteroscopy/
2 Hysteroscop$.tw.
3 uteroscop$.tw.
4 endoscop$ uter$.tw.
5 or/1-4
6 synchiolysis.tw.
7 Anti-adhesion$.tw.
8 exp tissue adhesion/
9 Adhesio$.tw.
10 sepracoat.tw.
11 icodextrin.tw.
12 hydrogel.tw.
13 hydrotubation.tw.
14 exp Hyaluronic Acid/
15 hyaluronic acid.tw.
16 oestrogen$.tw.
17 exp Intrauterine Devices/
18 (intrauterine adj2 device$).tw.
19 Ringer Lactate.tw.
20 Oxidized regenerated cellulose.tw.
21 Interceed$.tw.
22 Seprafilm$.tw.
23 polytetrafluoroethylene.tw.
24 Gore-tex$.tw.
25 spraygel$.tw.
26 Crystalloid$.tw.
27 Adept$.tw.
28 ACP gel$.tw.
29 Hyalobarrier gel$.tw.
30 intrauterine balloon.tw.
31 or/6-40
32 5 and 41
33 randomized controlled trial.pt.
34 controlled clinical trial.pt.
35 randomised.ab.
36 randomised.ab.
37 placebo.tw.
38 clinical trials as topic.sh.
39 randomly.ab.
40 trial.ti.
41 (crossover or cross-over or cross over).tw.
42 or/43-51
43 exp animals/ not humans.sh.
44 52 not 53
45 42 and 44
46 randomized controlled trial.pt.
47 controlled clinical trial.pt.
48 randomized.ab.
49 randomised.ab.
50 placebo.tw.
51 clinical trials as topic.sh.
52 randomly.ab.
53 trial.ti.
54 (crossover or cross-over or cross over).tw.
55 or/43-51
56 exp animals/ not humans.sh.
57 52 not 53
58 42 and 44
59 Last update 09/07/2013
Appendix 5. Web of Knowledge search strategy

# 20 #19 AND #18
# 19 TS =(randomized controlled trial)
# 18 #17 AND #13 AND #5
# 17 #16 OR #15 OR #14
# 16 TS =(reproductive outcome)
# 15 TS =(adhesion score)
# 14 TS =(intrauterine adhesions)
# 13 #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6
# 12 TS =(antibiotics)
# 11 TS =(intrauterine device)
# 10 TS =(oestrogen treatment)
# 9 TS =(amnion graft)
# 8 TS =(intrauterine balloon)
# 7 TS =(hyaluronic acid gel)
# 6 TS =(barrier agent)
# 5 #4 OR #3 OR #2 OR #1
# 4 TS =(synechiolysis)
# 3 TS =(operative hysteroscopy)
# 2 TS =(hysteroscopic surgery)
# 1 TS =(hysteroscopy)

Appendix 6. CINAHL search strategy

S1 (MM “Hysteroscopy”) OR “Hysteroscopy”
S2 (MH “Adhesions”) OR “adhesions”
S3 TX Adhesio*
S4 S2 OR S3
S5 S1 AND S4
EBSCO platform
Last update 10/07/2013

Appendix 7. Items of the pilot tested data extraction form

1. Source
   • study ID
   • report Id
   • reviewer author ID
   • citation and contact details

2. Eligibility
   • confirm eligibility for review
   • reason for exclusion

3. Trial characteristics

Study design
• random sequence generation
• patient recruitment
• patient in- and exclusion criteria
• allocation concealment
• blinding of participants, personnel and outcome assessors
• completeness of outcome data
• selective outcome reporting
• other potential sources of bias

Follow-up
• duration of follow-up
• type of follow-up

Size of study
• number of women recruited
• number of women randomised
• number of women excluded
• number of women withdrawn and lost to follow-up
• number of women analysed

Study setting
• single- centre or multicentre
• location
• timing and duration

Diagnostic criteria
• screening by TVS
• screening by HSG
• screening by TVS and HSG
• screening by other ultrasound diagnostic procedures, e.g. SIS or GIS
• screening by hysteroscopy
• diagnosis confirmed by hysteroscopy and biopsy

4. Characteristics of the study participants

Baseline characteristics
• age
• primary or secondary subfertility
• duration of subfertility
• diagnostic work-up: baseline FSH, semen analysis, diagnosis of tubal pathology, confirmatory test of ovulation
• other contributory causes to subfertility than uterine factor
• previous treatments - IVF, IUI or other treatments
Treatment characteristics
• IUI natural cycle
• IUI controlled ovarian stimulation with anti-oestrogens or gonadotropins
• IVF protocol and number of embryos transferred
• ICSI protocol and number of embryos transferred
• detailed description of the hysteroscopic procedure
• detailed description of the anti-adhesion therapy

5. Interventions

Total number of intervention groups

Absence of other interventions in the treatment and control group
For each intervention and comparison group of interest:
• specific intervention
• intervention details
• timing of the intervention

6. Outcomes

Outcomes and time points collected

Outcomes and time points reported
Definition and unit of measurement for each of the following outcomes:

Primary outcome:
• live birth
• incidence of de novo adhesion formation at second look hysteroscopy

Secondary outcome:
• clinical pregnancy
• miscarriage
• mean adhesion scores at second look hysteroscopy
• severity of adhesions at second look hysteroscopy

For each outcome of interest:
• sample size
• missing participants
• summary data for each intervention group in 2 x 2 table
• estimate of effect with 95% CI
• subgroup analyses
7. Miscellaneous

- funding source
- key conclusions of the study authors
- miscellaneous comments from the study authors
- references to other relevant studies
- correspondence required
- miscellaneous comments by the review authors

Contributions of Authors

JB conceived and developed the protocol.

JK co-authored the protocol for the background section.

SW, FB, TD and BMW all co-authored the protocol by giving overall advice on methodology and content.

Disclosures of Interest

None of the authors has any conflict of interest concerning the present research.

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  Logistical support by the Managing Secretary

External sources

- No sources of support supplied