Anti-adhesion therapy following operative hysteroscopy for treating female subfertility

Protocol information

Review number: JB1900

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What's new

Date	Event	Description

History

Date	Event	Description

Abstract

Background

Objectives

Search methods

Selection criteria

Data collection and analysis

Main results

Authors' conclusions

Plain language summary

[Summary title]

[Summary text]

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; 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 following incidences of postsurgical IUAs at second look hysteroscopy: 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/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-

~~The duration of the endometrial wound healing differs according to the type of pathology as reported by Yang and co-~~workers in a prospective cohort study of 163 women undergoing operative hysteroscopy (Yang 2013):~~. At second-look hysteroscopy one month after operative hysteroscopy, more women achieved a full healing of the endometrial cavity after removal of endometrial polyps (32/37 women or 86%) compared to adhesiolysis (30/45 women or 67%), metroplasty (3/16 women or 19%) or myomectomy (12/65 women or 18%) (P<0.05). Significantly more women suffered from novo IUAs at second look hysteroscopy after metroplasty (14/16 women or 88%) or adhesiolysis (34/45 women or 76%) compared to removal of submucous fibroids (26/65 women or 40%) or endometrial polyps (0/37 women or 0%). Women with de novo IUAs were less likely to achieve full endometrial wound healing within one month compared with those without adhesions (23/74 women or 31% versus 54/89 women or 61%, P=0.0003).~~ ~~T~~the authors ~~conclude~~reported that the time needed for a complete recovery of the endometrium ranges from one to three months, following respectively the hysteroscopic removal of endometrial polyps and submucous fibroids.

IUAs are associated with a poor reproductive outcome. Firstly, 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, 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, due to major and at times devastating obstetric complications, e.g. placenta accreta/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 ~~suggest the effectiveness of~~ different anti-adhesion strategies for preventing de novo adhesion formation following operative hysteroscopy.

IUD 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 8 observational studies (Deans 2010).~~The type of IUD may be important; copper-containing IUDs provoke an inflammatory reaction with probably 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 (e.g. Lippes loop) is generally considered the IUD of choice when treating IUAs; it is however no longer available in many countries (Kodaman 2007). At least 8 observational studies report the use of a Foley catheter for 3 to 10 days to act as a physical intrauterine barrier after surgical lysis of IUAs (Deans 2010).~~

Hormone therapy

In 1964, Wood and Pena suggested the use of oestrogen therapy to stimulate the regeneration of the endometrium after the surgical treatment of IUAs (Wood 1964). ~~Various regimens have been recommended with oestrogens (e.g. a typical daily dose of 2.5 mg of conjugated equine oestrogen twice daily for 30 days) with or without a progestin (e.g. 10 mg medroxyprogesterone acetate for 10 days) (Kodaman 2007); no comparative studies have been performed on dosage, administration, or combination of hormones (Deans 2010).~~

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 ß1-3-type glucoside bond. Solutions of HA have visco-elastic properties which have led to interests 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-cross-linked polysaccharide (ACP). It is formed by cross linking 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 cross linking, 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; it 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 the use 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 aim of anti-adhesion therapy is the maintenance of the uterine cavity by some physical means along with enhancement of endometrial growth.~~ The bulck 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- or observational studies.

IUD or Foley catheter balloon

The use of an IUD (13 observational studies) or a Foley catheter balloon (8 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 with probably 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 (e.g. Lippes loop) is generally considered the IUD of choice when treating IUAs; it is however no longer available in many countries (Kodaman 2007).~~Deans 2010~~.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 3 months (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 oestrogen 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 oestrogen (e.g. a typical daily dose of 2.5 mg of conjugated equine oestrogen twice daily for 30 days) with or without a progestin (e.g. 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 ~~randomized~~ to receive oestrogen and progestin or no treatment. Women in the intervention group had a significantly thicker endometrium (8.4 vs 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 concludeds that hormonal therapy, particularly oestrogen therapy, may be beneficial to women with IUAs but as an adjunctive therapy combined with other anti-adhesion strategies (Johary 2013).

Barrier gels

~~The ideal anti-adhesion adjunctive therapy following operative hysteroscopy would be the application of a biologically active mechanical separator that achieves the suppression on intrauterine adhesion formation and promotes the healing of the endometrium.~~ The use of the biodegradable gel surgical barriers is based on the principle of keeping the adjacent wound surfaces as 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 (Kelekci 2004; Rajab 2010) for preventing postsurgical adhesions. Other preclinical studies in animal models suggest that HA gel remains in situ for more than 5 to 6 days (Laurent 1992; Nimrod 1992). Similarly, animal studies demonstrate the persistence of HA-CMC for about 7 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 "hydroflotation" or "siliconizing" effects. One French clinical controlled trial (N=54 women) compares 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 are no statistically significant differences for the rate of adhesion formation between both 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 ~~patients~~ 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). Fresh HAM graft preserves its viability for 21 days following its application in the pelvic cavity (Trelford 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 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 the 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. This 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 2005). 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) evaluate~~s~~d 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 cost-effectiveness of both strategies was evaluated from the perspective of society and that of a third party payer. From the perspective of society, the HA-CMC strategy has a lower overall cost per woman of $1932 and a comparable effectiveness of 7.901 quality adjusted life years (QALYs) compared to the routine care strategy, which has a cost per woman of $3043 and effectiveness of 7.805 QALYs. From the perspective of a third party payer, the HA-CMC strategy has a similarly lower overall cost per woman of $1247 and comparable effectiveness of 7.987 QALYs versus the routine care strategy, which has a cost per woman of $1629 and effectiveness of 7.970 QALYs. The robustness of the clinical analysis model was confirmed by a several sensitivity analyses.~~ The authors conclude~~d~~ 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 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 ~~head-to-head versus~~ 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 (e.g. 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 randomi~~s~~zed women are the unit of analysis; only data from the first phase will be included in meta-analyses, as the crossover is not a valid study design in the context of subfertility.

Types of participants

Women of reproductive age ~~bound to~~ 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

~~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 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 case of unclear definitions. We will report any discrepancies in the final review.~~

~~There are at the present 7 reported classification systems for scoring the extent or severity of intrauterine adhesions. None of these systems has been validated or universally accepted (Deans 2010). We will therefore avoid pooling data from studies using different scoring systems; we will ask 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-look hysteroscopy was done between 4 to 12 weeks following operative hysteroscopy.~~

~~We will analyse data for the adverse events separately and not as one composite measure.~~

Primary outcomes

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

2. Adverse event: incidence of de novo adhesion formation at second look hysteroscopy.

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; it 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 gestational age (18 weeks post fertilization) or, if gestational age is unknown, the loss of an embryo/fetus of less than 400 grams.

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.

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We will analyse data for the adverse events separately and not as one composite measure.

~~We will generate a summary of findings (SoF) table for the main outcomes 'live birth or pregnancy' 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 GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias). Judgments about evidence quality (high, moderate or low) will be justified, documented, and incorporated into reporting of results for each outcome.~~

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 web sites 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 till 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 SIGN 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 till 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 till the present.
- National Guideline Clearinghouse (http://www.guideline.gov/) for evidence-based guidelines from inception till the present.
- BIOSIS previews through ISI Web of Knowledge (http://isiwebofknowledge.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 till 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 World Health Organization International Clinical Trials Registry Platform search portal (http://apps.who.int/trialsearch/) from inception till the present.
- 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 till the present.
- Conference abstracts and proceedings on the ISI Web of Knowledge (http://isiwebofknowledge.com) (Appendix 5) applying 'SCI-EXPANDED' and 'CPCI-S' from inception till 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&form=F) from inception till the present.
- European grey literature through Open Grey database from inception till the present (http://www.opengrey.eu/subjects/).
- 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 till the present.¬

Searching other resources

Two review authors (JB and JK) will hand search 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 hand search relevant journals and conference abstracts that are not covered in the MDSG register, in liaison with the Trials Search Co-ordinator. The search process will be reported in a PRISMA flow diagram in the review.

Data collection and analysis

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 will report the disagreement in the final review.~~The selection process will be documented with a "PRISMA" flow chart.~~

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. 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 derived from secondary papers. We will correspond with study investigators for further data on methods and/or 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 eligibility criteria will be excluded.

Assessment of risk of bias in included studies

Two reviewers (JB and SW) will independently assess the included studies for risk of bias using the Cochrane 'rRisk of bias assessment 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. In most surgical trials blinding of participants and personnel is almost impossible; a lack of blinding of participants and personnel may nevertheless increase the risk of bias even for unequivocal outcomes with an adequately long and complete follow-up. 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 Bbias' table, which will be incorporated into the interpretation of review findings by means of sensitivity analyses. We will consider the domains of allocation concealment, blinding of outcome assessors and incomplete outcome data to be the three single most important items for assessing the risk of bias for the present Cochrane review for two reasons. Firstly, these three domains have been consistently related to bias (Jüni 2001). Secondly, for randomised comparisons between an intervention and no intervention as in the present Cochrane review, strong beliefs regarding the benefits or risks of the allocated treatment are more likely to accepted than clinical equipoise, hence the importance given to allocation concealment and blinding of outcome assessment.

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)(http://www.cochrane.org/training/cochrane-handbook). It refers to the selective reporting of some outcomes (e.g. positive outcomes) and the failure to report others (e.g. 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 (e.g. 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 (e.g. 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 (e.g. adhesion scores) as continuous data. For ordinal data (e.g. adhesion scores), if all studies report exactly the same outcomes we will calculate mean difference (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 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 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 (e.g. 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 (e.g. 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 meta-analysed. Multiple live births (e.g. 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 outcomes (live birth) only; . Wwe will assume that live births would not have occurred in women without a reported outcome. For all other outcomes, we will only analyse the use an available data analysis. Any imputation undertaken for missing data on the primary outcomes will be subjected to sensitivity analysis (See:Sensitivity analysis).
If studies report sufficient detail to calculate mean differences but no information on associated standard deviation (SD), the outcome will be assumed to have standard deviation 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 I^2 statistic combined with the Q-statistic. Cochran's Q test, a kind of Chi^2 statistic, is the classical measure to test 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 Chi^2 distribution with k-1 degree of freedom where k is the number of studies. Q > k-1 suggests statistical heterogeneity. A low P value of Cochran's Q test means significant heterogeneous results among different studies; usually, the P value at 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 I^2 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 I^2 measurement greater than 50% will be taken to indicate substantial heterogeneity (Higgins 2003). We will explore possible explanations 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 results. Some types of reporting bias (e.g. publication bias, multiple publication bias, language bias etc) 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. ~~We aim to detect 'within study' reporting bias by seeking published protocols if available, and by comparing the outcomes between the protocol and the final published study report. Where identified studies fail to report the primary outcomes of live birth delivery but do report interim outcomes such as pregnancy, we will undertake informal assessment as to whether those reporting the primary outcomes have given typical values for the interim outcomes. 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.If there are ten 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).~~ If there are ten 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 ~~using~~ from the primary studies~~y~~ in a meta-analysis with Review Manager 5 ~~software~~ using ~~the~~ summary Mantel-Haenszel (M-H) odds ratios (ORs) ~~Peto Odds ratio~~ and a random-~~-~~effects model (REM) for the following 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.

The outcomes 'live birth' and 'clinical pregnancy' are considered positive outcomes of effectiveness and by 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 hysteroscopy are negative effects and higher numbers will be considered harmful. An increase in the odds of a particular outcome, which may be beneficial (e.g. live birth) or detrimental (e.g. 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, 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 be inevitably 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 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 restrictively even if enough data were available; subgroup analysis is by its nature an observational study which 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. 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-~~.irrespective of the trial quality; the distinction between "studies without high risk of bias" versus "all studies" will be based on the judgements for the three domains "allocation concealment", "blinding of outcome assessors" and "incomplete outcome data"; studies with an unclear or low risk of bias for all three domains will be assessed as "studies without high risk of bias"~~.
- a fixed-~~-~~effect rather than a random-~~-~~effects model had been adopted.
- alternative imputation strategies had been implemented.

- the summary effect measure was relative risk rather than odds ratio.

Grading the evidence

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 GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias). Judgments about evidence quality (high, moderate or low) will be justified, documented, and incorporated into reporting of results for each outcome.

Results

Description of studies

Results of the search

Included studies

Excluded studies

Risk of bias in included studies

Allocation (selection bias)

Blinding (performance bias and detection bias)

Incomplete outcome data (attrition bias)

Selective reporting (reporting bias)

Other potential sources of bias

Effects of interventions

Discussion

Summary of main results

Overall completeness and applicability of evidence

Quality of the evidence

Potential biases in the review process

Agreements and disagreements with other studies or reviews

Authors' conclusions

Implications for practice

Implications for research

Acknowledgements

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Ms.Elizabeth Bosselaers (Managing Secretary CEBAM, the Belgian Branch of the Dutch Cochrane Centre) for logistical support and language correction.

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.

Declarations of interest

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

Differences between protocol and review

Published notes

Characteristics of studies

Characteristics of included studies

Footnotes

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Other published versions of this review

Classification pending references

Data and analyses

Figures

Sources of support

Internal sources

- CEBAM, the Belgian Branch of the Dutch Cochrane Centre, Belgium
  Logistical support by the Managing Secretary

External sources

- No sources of support provided

Feedback

Appendices

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$.tw.
5 or/1-4
6 synechiolysis.tw.
7 Anti-adhesion$.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.
26 oestrogen$.tw.
27 exp Intrauterine Devices/
28 (intrauterine adj2 device$).tw.
29 Ringer Lactate.tw.
30 Oxidized regenerated cellulose.tw.
31 Interceed$.tw.
32 Seprafilm$.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.
40 intrauterine balloon.tw.
41 or/6-40
42 5 and 41

Last update 09/07/2013

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 "*Estrogens"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 26/06/2013

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$.tw.
26 oestrogen$.tw.
27 exp Intrauterine Devices/
28 (intrauterine adj2 device$).tw.
29 Ringer Lactate.tw.
30 Oxidized regenerated cellulose.tw.
31 Interceed$.tw.
32 Seprafilm$.tw.
33 polytetrafluoroethylene.tw.
34 Gore-tex$.tw.
35 spraygel$.tw.
36 Crystalloid$.tw.
37 Adept$.tw.
38 ACP gel$.tw.
39 Hyalobarrier gel$.tw.
40 intrauterine balloon.tw.
41 or/6-40
42 5 and 41
43 randomized controlled trial.pt.
44 controlled clinical trial.pt.
45 randomized.ab.
46 randomised.ab.
47 placebo.tw.
48 clinical trials as topic.sh.
49 randomly.ab.
50 trial.ti.
51 (crossover or cross-over or cross over).tw.
52 or/43-51
53 exp animals/ not humans.sh.
54 52 not 53
55 42 and 54

Last update 09/07/2013

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$.tw.
5 or/1-4
6 synechiolysis.tw.
7 Anti-adhesion$.tw.
8 exp tissue adhesion/
9 Adhesio$.tw.
10 sepracoat.tw.
11 icodextrin.tw.
12 hydrogel.tw.
13 hydrotubation.tw.
14 exp Hyaluronic Acid/
15 hyaluronic acid.tw.
16 intergel.tw.
17 Barrier Membrane$.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.
26 oestrogen$.tw.
27 exp intrauterine contraceptive device/

28 (intrauterine adj2 device$).tw.
29 Ringer Lactate.tw.
30 Oxidized regenerated cellulose.tw.
31 Interceed$.tw.
32 Seprafilm$.tw.
33 polytetrafluoroethylene.tw.
34 Gore-tex$.tw.
35 spraygel$.tw.
36 Crystalloid$.tw.
37 Adept$.tw.
38 ACP gel$.tw.
39 Hyalobarrier gel$.tw.
40 intrauterine balloon.tw.
41 or/6-40
42 5 and 41
43 Clinical Trial/
44 Randomized Controlled Trial/
45 exp randomisation/
46 Single Blind Procedure/
47 Double Blind Procedure/
48 Crossover Procedure/
49 Placebo/
50 Randomi?ed controlled trial$.tw.
51 Rct.tw.
52 random allocation.tw.
53 randomly allocated.tw.
54 allocated randomly.tw.
55 (allocated adj2 random).tw.
56 Single blind$.tw.
57 Double blind$.tw.
58 ((treble or triple) adj blind$).tw.
59 placebo$.tw.
60 prospective study/
61 or/43-60
62 case study/
63 case report.tw.
64 abstract report/ or letter/
65 or/62-64
66 61 not 65
67 42 and 66

Last update 09/07/2013

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)

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

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