Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility (Review)

Bosteels J, Weyers S, Kasius J, Broekmans FJ, Mol BWJ, D'Hooghe TM

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2015, Issue 11

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Jan Bosteels[1], Steven Weyers[2], Jenneke Kasius[3], Frank J Broekmans[3], Ben Willem J Mol[4], Thomas M D'Hooghe[5]

[1]Belgian Branch of the Dutch Cochrane Centre, Leuven, Belgium. [2]Obstetrics and Gynaecology, University Hospital Ghent, Ghent, Belgium. [3]Department of Reproductive Medicine and Gynecology, University Medical Center, Utrecht, Netherlands. [4]The Robinson Institute, School of Paediatrics and Reproductive Health, The University of Adelaide, Adelaide, Australia. [5]Leuven University Fertility Centre, University Hospital Gasthuisberg, Leuven, Belgium

Contact address: Jan Bosteels, Belgian Branch of the Dutch Cochrane Centre, Kapucijnenvoer 33 blok J bus 7001, 3000 Leuven, Leuven, Belgium. Jan.bosteels@med.kuleuven.be. jan.bosteels@hotmail.com.

Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: New, published in Issue 11, 2015.
Review content assessed as up-to-date: 1 March 2015.

Citation: Bosteels J, Weyers S, Kasius J, Broekmans FJ, Mol BWJ, D'Hooghe TM. Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility. *Cochrane Database of Systematic Reviews* 2015, Issue 11. Art. No.: CD011110. DOI: 10.1002/14651858.CD011110.pub2.

ABSTRACT

Background

Limited observational evidence suggests potential benefit for subfertile women undergoing operative hysteroscopy with several anti-adhesion therapies (e.g. insertion of an intrauterine device (IUD) or balloon, hormonal treatment, barrier gels or human amniotic membrane grafting) to decrease intrauterine adhesions (IUAs).

Objectives

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

Search methods

We searched the following databases from inception to March 2015: the Cochrane Menstrual Disorders and Subfertility Specialised Register, the Cochrane Central Register of Controlled Trials (2015, Issue 2), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and other electronic sources of trials, including trial registers, sources of unpublished literature and reference lists. We handsearched *The Journal of Minimally Invasive Gynecology,* and we contacted experts in the field.

Selection criteria

Randomised comparisons of anti-adhesion therapies versus placebo, no treatment or any other anti-adhesion therapy following operative hysteroscopy in subfertile women. The primary outcome was live birth or ongoing pregnancy. Secondary outcomes were clinical pregnancy, miscarriage and IUAs present at second look, along with their mean adhesion scores or severity.

Data collection and analysis

Two review authors independently selected studies, assessed risk of bias, extracted data and evaluated quality of the evidence using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) method.

Main results

We included 11 randomised studies on use of an inserted device versus no treatment (two studies; 84 women) or another inserted device (one study; 162 women), hormonal treatment versus no treatment or placebo (two studies; 131 women), gel versus no treatment (five studies; 383 women) and graft versus no graft (one study; 43 women). The total number of women randomly assigned was 924, but data on only 803 participants were available for analysis. The proportion of subfertile women varied from 0% (one study; 41 women), to less than 50% (six studies; 487 women), to 100% (one study; 43 women); the proportion was unknown in three studies (232 women). Most studies (9/11) were at high risk of bias with respect to one or more methodological criteria.

We found no evidence of differences between anti-adhesion therapy and no treatment or placebo with respect to live birth rates (odds ratio (OR) 0.99, 95% confidence interval (CI) 0.46 to 2.13, P value = 0.98, three studies, 150 women; low-quality evidence) and no statistical heterogeneity (Chi^2 = 0.14, df = 2 (P value = 0.93), I^2 = 0%).

Anti-adhesion therapy was associated with fewer IUAs at any second-look hysteroscopy when compared with no treatment or placebo (OR 0.36, 95% CI 0.20 to 0.64, P value = 0.0005, seven studies, 528 women; very low-quality evidence). We found no statistical heterogeneity (Chi^2 = 2.65, df = 5 (P value = 0.75), I^2 = 0%). The number needed to treat for an additional beneficial outcome (NNTB) was 9 (95% CI 6 to 20).

No evidence suggested differences between an IUD and an intrauterine balloon with respect to IUAs at second-look hysteroscopy (OR 1.23, 95% CI 0.64 to 2.37, P value = 0.54, one study, 162 women; very low-quality evidence).

Authors' conclusions

Implications for clinical practice

The quality of the evidence retrieved was low or very low for all outcomes. Clinical effectiveness of anti-adhesion treatment for improving key reproductive outcomes or for decreasing IUAs following operative hysteroscopy in subfertile women remains uncertain.

Implications for research

Additional studies are needed to assess the effectiveness of different anti-adhesion therapies for improving reproductive outcomes in subfertile women treated by operative hysteroscopy.

PLAIN LANGUAGE SUMMARY

Anti-adhesion treatment after hysteroscopy for women having difficulty becoming pregnant

Review question

To assess the effects of treatments for prevention of scar tissue after surgical treatment for lesions of the womb in women having difficulty becoming pregnant.

Background

The present practice used to prevent scar tissue formation after surgery of the cavity of the womb is based on traditional or observational studies.

Search date

Evidence is current to 1 March 2015.

Study characteristics

We searched for studies that randomly compared any treatment versus no treatment, placebo or any other intervention in women having difficulty becoming pregnant after surgery for abnormalities of the cavity of the womb. Outcomes were live birth or ongoing pregnancy, clinical pregnancy, miscarriage and presence or severity of scar tissue at the second-look procedure.

Study funding sources

Six studies received no external funding, the government funded one study and four studies provided unclear information on funding.

Key results

We found 11 studies. Treatments included insertion of a device compared with no treatment (two studies; 84 women) or insertion of another device (one study; 162 women), intake of hormonal tablets after surgery (two studies; 131 women), use of sticky gels (five studies; 383 women) and application of membranes of the afterbirth of newborn babies (one study; 43 women). Investigators randomly assigned 924 women, but data on only 803 women were available for analysis. The proportion of women having difficulty becoming pregnant varied from 0% (one study; 41 women), to less than 50% (six studies; 487 women), to 100% (one study; 43 women); the proportion was not known in three studies (232 women). Most studies (9/11) were at high risk of bias in one or more areas. No proof shows benefit with any anti-adhesion treatment for increasing the chance of a liveborn baby (three studies; 150 women). Use of sticky gels (five studies; 383 women) can diminish the presence of scar tissue: We would expect that out of 1000 women treated by surgery of the womb, between 120 and 316 would develop scar tissue after using sticky gels, compared with 454 women when no gels were used. No proof indicates that inserting a contraceptive coil may decrease scar tissue better than inserting a balloon.

Quality of the evidence

The overall quality of study evidence is low or very low for all outcomes. More research is needed before anti-adhesion treatment can be routinely offered after hysteroscopic treatment to women having difficulty becoming pregnant.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Any anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility vs no treatment or placebo

Patient or population: women treated by operative hysteroscopy for uterine pathology associated with subfertility or adverse pregnancy outcome
Settings: single centre - Hysteroscopy Unit or Department of Obstetrics and Gynaecology of a university or non-university tertiary care hospital
Intervention: any anti-adhesion therapy
Comparison: no treatment or placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No treatment	Anti-adhesion treatment				
Live birth	**Average-risk population**[a]		**OR 0.99** (0.46 to 2.13)	150 (3 studies)	⊕⊕◯◯ **Low**[b,c,d,e]	
	338 per 1000	**292 per 1000 (182 to 469)**				
Presence of intrauterine adhesions at any second-look hysteroscopy - anti-adhesion barrier gels (second-look hysteroscopy at 4 to 12 weeks after operative hysteroscopy)	**Low-risk population**[f]		**OR 0.37** (0.20 to 0.67)	383 (5 studies)	⊕◯◯◯ **Very low**[e,g,h]	
	0 per 1000	**0 per 1000**				
	Medium-risk population[f]					
	454 per 1000	**194 per 1000 (120 to 316)**				
	High-risk population[f]					
	875 per 1000	**374 per 1000 (231 to 608)**				

Presence of intrauterine adhesions at any second-look hysteroscopy - other anti-adhesion therapy (second-look hysteroscopy at 4 to 8 weeks after operative hysteroscopy)	**Low-risk population**[f]		**OR 0.14** (0.01 to 2.72)	145 (2 studies)	⊕⊕◯◯ **Low**[e,i,j,k,l,m]
	0 per 1000	**0 per 1000**			
	Medium-risk population[f]				
	454 per 1000	**66 per 1000 (3 to 1250)**			
	High-risk population[f]				
	875 per 1000	**127 per 1000 (7 to 2410)**			

*The basis for the **assumed risk** is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Assumed risk for average-risk population is the risk of live birth in pooled control groups of the 3 included studies.
[b] Two studies at high risk of bias, and the third study at low risk of bias; a sensitivity analysis on the choice to include all 3 studies regardless of study quality compared with the single study at low risk of bias revealed no substantial change in direction or magnitude of effect size and in tests of statistical significance.
[c] Indirectness of evidence: Only a portion of participants suffered from subfertility in 2 included studies.
[d] Results of 2 studies imprecise, given wide confidence intervals.
[e] Formal study of reporting bias not possible.
[f] Assumed risk for low/medium/high-risk population based on presence of intrauterine adhesions following hysteroscopic removal of endometrial polyps/mean prevalence of IUAs/removal of uterine septum, respectively, based on findings of a prospective cohort study.
[g] Design of the 5 studies had several main limitations.
[h] Substantial indirectness of available evidence: in 2 of 4 Italian trials, <50% of participants suffered from subfertility; in 2 other Italian studies, subfertile women were included even after clarifying with primary study authors; and in the fifth trial from Israel, only women with proven fertility were included.

[i] Small study with no events resulting in undetermined treatment effects.
[j] High risk of performance and detection bias because participants, personnel and outcome assessors were not blinded. Moreover, concern surrounds imbalance in baseline characteristics between comparison groups; the proportion of women with IUAs was higher in the intervention group (17/31) than in the control group (10/31).
[k] Not clear whether subfertile women were included, and if so, how many.
[l] Indirectness of available evidence: only 34% of participants suffering from subfertility.
[m] Imprecision: confidence intervals of effect estimate very wide.

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 complete obliteration of the uterine cavity. Any trauma to the endometrium (the inner layer of the uterus) can lead to formation of IUAs; in daily clinical practice, nearly 90% of all IUAs are associated with postpartum or postabortion dilatation and curettage (Nappi 2007). The aetiological role of infection in the formation of IUAs is controversial, with the exception of genital tuberculosis (Deans 2010). IUA formation is the major long-term complication of hysteroscopic surgery in women of reproductive age.

Several intrauterine anomalies have been linked with female subfertility (Bosteels 2015). Endometrial polyps are benign, endometrial, stalk-like masses protruding into the uterine cavity. Fibroids are excessive growths originating from the muscular portion of the uterine cavity. A septate uterus is a congenital malformation in which the longitudinal band separating left and right Müllerian ducts, which form the uterus in the human female foetus, has not been entirely resorbed. Hysteroscopy allows direct visualisation of the uterine cavity through a rigid, semi-rigid or flexible endoscope. The hysteroscope consists of a rigid telescope with a proximal eyepiece and a distal objective lens that may be angled at 0 degrees to allow direct viewing, or offset at various angles to provide a fore-oblique view. Operative hysteroscopy requires adequate visualisation through continuous fluid circulation using inflow and outflow channels. The sheath system of the operative hysteroscope contains one or two 1.6- to 2.0-mm working channels for insertion of a small grasping or biopsy forceps, scissors, myoma fixation instruments, retraction loops, morcellators (surgical instruments used to divide and remove tissue during endoscopic surgery) and aspiration cannulae or unipolar or bipolar electrodiathermy instruments. Operative hysteroscopic procedures require a complex instrumentation setup, special training of the surgeon and appropriate knowledge and management of complications. Removal of endometrial polyps by an endoscope is called hysteroscopic polypectomy. Hysteroscopic myomectomy is the procedure by which a fibroid is removed by hysteroscopy. Removal of a uterine septum is termed hysteroscopic septoplasty or septum resection. Removal of IUAs is called hysteroscopic adhesiolysis or synechiolysis. A diagnostic or operative hysteroscopy following an operative hysteroscopy is termed a second-look hysteroscopy.

A randomised controlled trial (RCT) reported the following numbers for the incidence 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). 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 in rodents, may have an important function for 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 endometrial wound healing depends on the type of pathology present, according to a prospective cohort study of 163 women undergoing operative hysteroscopy (Yang 2013); these investigators reported that the time needed for complete recovery of the endometrium ranges from one to three months following hysteroscopic removal of endometrial polyps and submucous fibroids, respectively.

IUAs are associated with poor reproductive outcomes. This is due in part to infertility, with prevalence as high as 43% (922 of 2151 women) according to a large review of observational studies (Schenker 1982). Poor outcomes also result from the clinical problem of recurrent miscarriage, ranging from 5% to 39% in women with IUAs, according to a review of observational studies (Kodaman 2007), and from major and at times devastating obstetrical complications, for example, placenta accreta or increta, as well as higher risks for preterm delivery, uterine rupture and peripartum hysterectomy as the endpoint of successful hysteroscopic treatment for severe IUAs (Deans 2010).

Description of the intervention

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

Intrauterine device

An intrauterine device (IUD) may provide a physical barrier between the uterine walls, separating the endometrial layers after lysis of IUAs. Its insertion as an adjunct therapy for the prevention of IUAs 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).

Hormonal therapy

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

Barrier gels

Hyaluronic acid (HA) or hyaluronan is a water-soluble polysaccharide that consists of multiple disaccharide units of glucuronic acid and N-acetylglucosamine bound together by a β1-3-type glucoside bond. Solutions of HA have viscoelastic properties that have

led to interest in developing applications of HA in surgical procedures, for example, during eye surgery, and for prevention of postsurgical adhesions. However, HA may not be the ideal substance for all procedures because of its limited residence time when applied to a surgical site. It quickly enters the systemic circulation, then is cleared rapidly by catabolic pathways. Attempts to use HA for prevention of postsurgical adhesions have therefore resulted in 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), which is formed by cross-linking of HA via direct formation of co-valent ester bonds between hydroxyl and carboxyl groups of the hyaluronan molecule. ACP can be prepared through various degrees of cross-linking: This allows tailoring of the viscosity properties of ACP gels (Renier 2005). Carboxymethylcellulose (CMC) is a high-molecular-weight polysaccharide that has greater viscosity than dextran 70. CMC can be used for adhesion prevention as a membrane barrier, or as a gel attained by mixing chemically derivative sodium hyaluronate and carboxymethylcellulose gel (HA-CMC) (Leach 1998).

Human amniotic membrane grafting

Over the past three decades, the surgical community has become more aware of the increasing potential of human amniotic membrane (HAM) as an adjunctive anti-adhesion intervention. Whole human foetal membranes or amnion alone has been used in surgery 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 as a graft in forming an artificial vagina, as a barrier in preventing postoperative intra-abdominal adhesion formation and, finally, as a biological dressing following radical vulvectomy or groin dissection (Amer 2006).

How the intervention might work

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

Intrauterine device

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

Hormonal therapy

Many studies recommend use of a cyclical oestrogen and progestogen treatment regimen following hysteroscopic treatment of IUAs to promote regeneration of the endometrium (Deans 2010). Various regimens consisting of oestrogen (e.g. 2.5 mg conjugated equine oestrogen twice daily for 30 days) with or without a progestogen (e.g. 10 mg medroxyprogesterone acetate for 10 days) have been proposed (Kodaman 2007). No comparative studies have been performed to examine dosage, administration or combinations of hormones (Deans 2010). In an RCT (Farhi 1993), 60 women undergoing dilatation and curettage during the first trimester of pregnancy were allocated to receive oestrogen combined with progestogen, or no treatment. Women in the intervention group had a significantly thicker endometrium (8.4 vs 6.7 mm; P value = 0.02) compared with those in the control group. Study authors concluded that postoperative hormonal treatment may be beneficial for IUA prevention following surgical trauma to the uterine cavity. Nevertheless, they provided no data on pregnancy outcomes or IUA recurrence (Farhi 1993). A systematic review of 26 observational studies concluded that hormonal therapy, particularly oestrogen treatment, may be beneficial for women with IUAs, but as adjunctive therapy combined with other anti-adhesion strategies (Johary 2013).

Barrier gels

Use of biodegradable gel surgical barriers is based on the principle of keeping adjacent wound surfaces mechanically separate (Renier 2005). Several preclinical studies in various animal models have demonstrated the effectiveness of 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 of HA-CMC membranes (Kelekci 2004; Rajab 2010), for preventing postsurgical adhesions. Other

preclinical studies in animal models suggest that HA gel remains in situ longer 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 re-formation are not well known but may be related to 'hydroflotation' or 'siliconizing' effects. One French CCT (N = 54 women) compared application of ACP gel (N = 30) versus no gel (N = 24) at the end of an operative hysteroscopic procedure performed to treat myomas, polyps, uterine septa or IUAs; investigators reported no statistically significant differences between comparison groups in the rate of adhesion formation, nor in mean adhesion scores and severity of adhesions (Ducarme 2006). They provided no data on reproductive outcomes.

Human amniotic membrane grafting

Preclinical data on the effectiveness of HAM grafting in different animal models present conflicting results. One trial (Szabo 2002) demonstrated a beneficial effect in preventing de novo (new) adhesions, whereas two other animal studies (Arora 1994; Badawy 1989) reported that HAM grafting fails to prevent IUAs. One observational study provided data on use of a fresh amniotic graft over an inflated Foley catheter balloon to prevent recurrence of IUAs after hysteroscopic lysis in 25 women with moderate to severe Asherman syndrome. Minimal adhesion re-formation was demonstrated in 48% of study participants with severe adhesions. Study authors concluded that HAM grafting might be promising as adjunctive therapy following hysteroscopic adhesiolysis; it acts as a biologically active mechanical barrier to suppress adhesion formation while promoting endometrial healing (Amer 2006). A fresh HAM graft preserves its viability for 21 days following application in the pelvic cavity (Trelford Sauder 1977). In addition to serving as an anatomical barrier, HAM may promote the regeneration of epithelium by acting as a basement membrane substrate; HAM may also facilitate migration of epithelial cells, reinforce adhesion of the basal epithelium, promote epithelial cell differentiation (Meller 1999) and prevent cellular apoptosis (Hori 2006). Human amniotic 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, whether anti-adhesion therapies after operative hysteroscopy might be beneficial for the outcome of pregnancy or live birth is not known. Providing a summary and critical appraisal of existing evidence on the effectiveness of different anti-adhesion treatments in subfertile women after operative hysteroscopy is the main objective of this Cochrane review. Moreover, little is known about the relative contributions of different anti-adhesion strategies toward increasing reproductive benefit in women wishing to conceive following operative hysteroscopy; performing this head-to-head comparison of alternative anti-adhesion interventions is a secondary objective of the present research.

Adhesions may cause infertility, abdominal pain or bowel obstruction. The healthcare burden associated with these three clinical problems is substantial (DeCherney 1997; diZerega 1994; Renier 2005). The total cost of adhesion-related morbidity for the US Health Care System exceeds $1 billion annually (Baakdah 2005). One trial in the domain of gynaecological oncology (Bristow 2007) evaluated the cost-effectiveness of an HA-CMC anti-adhesion barrier versus routine care, during which no adhesion prevention measures were taken, by applying a decision analysis model in the setting of women undergoing radical hysterectomy and pelvic lymphadenectomy for stage IB cervical cancer. Study authors concluded that given a conservative set of clinical and economic assumptions, an adhesion prevention strategy utilising an HA-CMC barrier in women undergoing radical hysterectomy for stage IB cervical cancer might be cost-effective from the perspective of society and from the view of a third party payer. To the best of our knowledge, no cost-effectiveness studies have explored adhesion prevention after operative hysteroscopy in an infertile population; evidence retrieved through the present research could serve as the basis for economical studies of different anti-adhesion treatments. This is another secondary objective of the present review.

Infertility, defined as the inability to conceive after a defined period of unprotected intercourse, is an often neglected aspect of reproductive health worldwide. Official ways of providing assistance for reproductive health care and family planning are few 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). Reproductive health has long been recognised by the World Health Organization as a priority global health topic (http://www.who.int/topics/reproductive_health/en/).

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished parallel-group randomised controlled trials (RCTs) were eligible for inclusion. We excluded non-randomised studies (e.g. studies with evidence of inadequate sequence generation such as alternate days, participant numbers), as they are associated with high risk of bias. We planned to include cross-over trials if individually randomly assigned women were the unit of analysis; we aimed to include in the meta-analyses data from the first phase only, as the cross-over 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 in which at least a proportion of women were undergoing operative hysteroscopy for subfertility were eligible. Studies excluding women wishing to conceive were not eligible.

Types of interventions

We included the following randomly assigned comparisons.

- Anti-adhesion therapy versus placebo or no treatment following operative hysteroscopy.
- Anti-adhesion therapy A versus anti-adhesion therapy B following operative hysteroscopy.

Types of outcome measures

Primary outcomes

- Live birth or ongoing pregnancy
  - Live birth was defined as delivery of at least one live foetus 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.
  - Ongoing pregnancy was defined as pregnancy surpassing the first trimester or 12 weeks of pregnancy and will be used as a surrogate outcome for live birth. Term delivery, defined as birth at any time between three weeks before and two weeks after the expected date of delivery (37 to 42 weeks of gestation) will also be used as a surrogate outcome for live birth.

Secondary outcomes

- Clinical pregnancy, defined as pregnancy diagnosed by ultrasonographic visualisation 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.
- Miscarriage, defined as spontaneous loss of a clinical pregnancy that occurs before 20 completed weeks of gestation (18 weeks post fertilisation) or, if gestational age is unknown, loss of an embryo or foetus of less than 400 G.
- Presence of IUAs at second-look hysteroscopy.
- Mean adhesion scores at second-look hysteroscopy.
- Severity of adhesions at second-look hysteroscopy.

We did not exclude studies on the basis of their reported outcome measures. We reviewed eligible studies that could have measured the outcomes of interest; we aimed to report in the final review any lack of data for the key outcomes.

We adhered as much as possible to terminology of the International Committee for Monitoring Assisted Reproductive Technology (ICMART) (http://www.icmartivf.org/) for key reproductive outcomes (live birth, pregnancy and miscarriage) (Zegers-Hochschild 2009); we contacted primary study authors for clarification in cases of unclear definitions. We reported discrepancies or uncertainties in the final review.

At present, seven classification systems are reported for scoring the extent or severity of IUAs. None of these systems have been validated or universally accepted (Deans 2010). We therefore avoided pooling data from studies using different scoring systems, and we asked for clarification from primary study authors, when necessary.

According to a prospective cohort study, the duration of endometrial wound healing may be different according to the type of pathology; study authors concluded that recovery of the endometrium may vary from one month (after hysteroscopic removal of polyps) to three months (following hysteroscopic myomectomy) (Yang 2013). We planned to pool studies when assessment of IUAs by second-look hysteroscopy was done between four and 12 weeks after operative hysteroscopy.

We analysed data for adverse events separately and not as one composite measure.

Search methods for identification of studies

We searched for all published and unpublished RCTs of anti-adhesion therapies following operative hysteroscopy in subfertile women, with no language restrictions and in consultation with the Gynaecology and Fertility Group (CGF) Trials Search Co-ordinator.

Electronic searches

We searched the following electronic databases, trial registers and websites using the search strategies provided in the appropriate appendices: the Menstrual Disorders and Subfertility Group (MDSG) Specialised Register (3 March 2015) (Appendix 1), the Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 2) (Appendix 2), MEDLINE using PubMed (1950 to 1 March 2015) (Appendix 3) and EMBASE using EMBASE.com (1974 to 1 March 2015) (Appendix 4).

The search strategy combined both index and free-text terms.

Our MEDLINE search included the Cochrane highly sensitive search strategy for identifying randomised trials as it appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (http://www.cochrane.org/training/cochrane-handbook).

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

Electronic sources of trials included the following.

- Cochrane Central Register of Controlled Trials (CENTRAL).
- Cochrane Database of Systematic Reviews (CDSR) (2015, Issue 2).
- 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 to 1 March 2015).
- National Guideline Clearinghouse (http://www.guideline.gov/) for evidence-based guidelines (from inception to 1 March 2015).
- Citations, conference abstracts and proceedings in the Institute for Scientific Information (ISI) Web of Science (WoS) core collection, Biosis Previews and Biosis Citation Index through WoS (http://wcs.webofknowledge.com.kuleuven.ezproxy.kuleuven.be) (from inception to 1 March 2015) (Appendix 5) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) (http://web.b.ebscohost.com.kuleuven.ezproxy.kuleuven.be) (from inception to 1 March 2015) (Appendix 6) through EBSCOHost, available at the Biomedical Library Gasthuisberg of the Catholic University of Leuven.
- Trial registers for ongoing and registered trials: ISRCTN Registry (http://www.isrctn.com/) and World Health Organization (WHO) International Clinical Trials Registry Platform search portal (http://apps.who.int/trialsearch/) (from inception to 1 March 2015).
- Latin American Caribbean Health Sciences Literature (LILACS) database, which is a source of trials from the Spanish and Portuguese speaking world (http://lilacs.bvsalud.org/en/) (from inception to 1 March 2015).
- European grey literature through the Open Grey database (http://www.opengrey.eu/) (from inception to 1 March 2015).
- General search engines Turning Research Into Practice (TRIP) database (http://www.tripdatabase.com/), Google Scholar (http://scholar.google.com/) and Scopus, available at the Biomedical Library Gasthuisberg of the Catholic University of Leuven (http://www-scopus-com.kuleuven.ezproxy.kuleuven.be) (from inception to 1 March 2015).

Searching other resources

Two review authors (JB and JK) handsearched reference lists of articles retrieved by the search and contacted experts in the field to request additional data. We contacted the first or corresponding authors of included studies to ascertain whether they were aware of any ongoing or unpublished trials. We handsearched *The Journal of Minimally Invasive Gynecology* (from inception to 1 March 2015) to look for conference abstracts that are not covered in the MDSG Specialised Register, in liaison with the Trials Search Coordinator. We documented the search process in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram in the final review.

Data collection and analysis

Selection of studies

After an initial screen of titles and abstracts retrieved by the search, as conducted by JB, we retrieved the full texts of all potentially eligible studies. Two review authors (JB and JK) independently examined these full-text articles for compliance with the inclusion criteria and selected studies eligible for inclusion in the review. We corresponded with study investigators, as required, to clarify study eligibility. We resolved disagreements as to study eligibility by discussion or by consultation with a third review author (BWM). We classified the study as 'awaiting classification' if disagreements between review authors were not resolved, and we reported disagreements in the final review.

Data extraction and management

At least two review authors (JB as a methodologist and TD/FB/JK/SW as content experts) independently extracted data from all eligible studies using a data extraction form designed and pilot-tested by the review authors. We resolved disagreements by discussion or by consultation with a third review author (BWM). Extracted data included study characteristics and outcome data (Appendix 7). When studies had multiple publications, we collated multiple reports on the same study, so that each study rather than each report was the unit of interest in the review, and we assigned such studies a single study ID with multiple references. We used the main trial report as the reference and derived additional details from secondary papers. We corresponded with study investigators to request further data on methods and results, as required. We included studies irrespective of whether outcomes were reported in a 'usable' way. In multi-arm studies, we excluded data from arms that did not meet the eligibility criteria.

Assessment of risk of bias in included studies

At least two review authors (JB and TD/FB/JK/SW) independently assessed included studies for risk of bias using the Cochrane risk of bias tool (http://www.cochrane.org/training/cochrane-handbook). We assessed the following seven items: 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 resolved disagreements by discussion or by consultation with a third review author (BWM). We fully described all judgements and presented our conclusions in the 'Risk of bias' table, which we incorporated into our interpretation of review findings by conducting 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). This term refers to selective reporting of some outcomes (e.g. positive outcomes) and failure to report others (e.g. adverse events). We took care to search for within-trial selective reporting, such as trials failing to report obvious outcomes, or failing to report them in insufficient detail to allow inclusion. We looked for published protocols and compared outcomes between the protocol and the final published study. When identified studies failed to report the primary outcome of live birth but did report interim outcomes such as pregnancy, we planned to undertake informal assessment as to whether the interim values (e.g. pregnancy rates) were similar to those reported in studies that also reported live births.

If any outcomes were defined in the protocol or the study report, and data were insufficient to allow inclusion, we sought to mention this lack of data along with the suggestion that additional clinical trials need to be conducted to clarify these knowledge gaps.

Measures of treatment effect

For dichotomous data (e.g. live births, clinical pregnancy rates), we used the numbers of events in control and intervention groups of each study to calculate Mantel-Haenszel odds ratios (ORs). We treated ordinal data (e.g. adhesion scores) as continuous data. For ordinal data (e.g. adhesion scores), if all studies reported exactly the same outcomes, we calculated mean differences (MDs) between treatment groups. If similar outcomes were reported on different scoring scales, we did not calculate standardised mean differences (SMDs) because the seven different adhesion score classifications had not been validated. We aimed to reverse the direction of effect of individual studies, if required, to ensure consistency across trials. We presented 95% confidence intervals (CIs) for all outcomes and contacted corresponding or first authors of all included trials that reported data in a form that was not suitable for meta-analysis, for example, time-to-pregnancy (TTP) data. We reported data from reports that failed to present additional data that could be analysed under 'other data'. We did not include TTP data in any meta-analysis. When data were not available for calculating ORs or MDs, we planned to utilise the most detailed numerical data provided that might facilitate similar analyses of included studies (e.g. test statistics, P values). We compared the magnitude and direction of effect reported by studies with how they were presented in the review, while taking account of legitimate differences.

Unit of analysis issues

We performed the primary analysis per woman randomly assigned; however, we included per-pregnancy data for one secondary outcome (miscarriage). If studies reported only per-cycle data, we planned to contact primary study authors to request per-woman data. If these were not available, we planned to briefly summarise per-cycle data in an additional table without performing a meta-analysis. We counted multiple live births (e.g. twins, triplets) as one live birth event only. We planned to include only first-phase data from cross-over trials if retrieved and found eligible.

Dealing with missing data

We planned to analyse data on an intention-to-treat basis as far as possible; if needed, we attempted to obtain missing data from the original researchers. When these could not be obtained, we planned to undertake imputation of individual values for the beneficial primary outcome only (live birth); we assumed that live births would not have occurred in women without a reported outcome. For all other outcomes, we analysed only available data. We subjected any imputation undertaken for missing data for the primary outcome to sensitivity analysis. (See Sensitivity analysis.) If studies reported sufficient detail to calculate mean differences but did not provide information on associated standard deviations (SDs), we assumed that the outcome had an SD equal to the highest SD from other studies within the same analysis.

Assessment of heterogeneity

We planned to consider carefully whether clinical and methodological characteristics of included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We carried out a formal assessment of statistical heterogeneity by using the I^2 statistic combined with the Q-statistic. Cochran's Q test, a form of Chi^2 statistic, is the classical measure used 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 Chi^2 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 indicates significantly heterogeneous results among different studies; usually a P value of 0.10 is used as the cutoff. 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 of the presence or absence of heterogeneity; it does not reveal the extent of such heterogeneity. The I^2 statistic describes the percentage of variation across studies that is due to significant heterogeneity rather than to random chance. It measures the extent of heterogeneity. An I^2 value greater than 50% was taken to indicate substantial heterogeneity (Higgins 2003). We planned to explore possible explanations for heterogeneity when substantial.

Assessment of reporting biases

Reporting biases arise when 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) 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 aimed to minimise their potential impact by ensuring a comprehensive search for eligible studies and by staying alert for duplication of data.

If 10 or more studies were to be included in an analysis, we planned to 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) entered the data and carried out all statistical analyses of the data in Review Manager 5. When studies were sufficiently similar and substantial statistical heterogeneity could be confidently ruled out, we combined data derived from primary studies in a meta-analysis using Review Manager 5; we used summary Mantel-Haenszel (M-H) ORs and a random-effects model (REM) for the following comparisons.

- Anti-adhesion therapy versus placebo or no treatment following operative hysteroscopy.

- Anti-adhesion therapy A versus anti-adhesion therapy B following operative hysteroscopy.

We considered outcomes of 'live birth' and 'clinical pregnancy' positive outcomes of effectiveness; as a consequence, we considered higher numbers as a benefit. Outcomes of 'miscarriage' and 'presence of IUAs' or 'mean adhesion scores' or 'severity of adhesions' at second-look hysteroscopy are negative effects, and we considered higher numbers as harmful. An increase in the odds of a particular outcome that may be beneficial (e.g. live birth) or detrimental (e.g. IUAs) was 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 aimed to define analyses that were comprehensive and mutually exclusive, so all eligible study results could be slotted into only one stratum in each comparison, and so trials within the same stratum could be sensibly pooled. Stratification was not a requirement, but it allowed consideration of effects within each stratum as well as, or instead of, an overall estimate for the comparison. Use of an REM instead of a fixed-effect model (FEM) was justified by the fact that results of similar surgical treatments may be different across studies; despite rigorous standardisation, differences in surgical skill might be inevitable among the different surgeons involved in clinical trials. If we retrieved no RCTs for some comparisons, we indicated their absence in the review as revealing knowledge gaps for which further research is needed. We planned to present a narrative overview if meta-analysis was not appropriate.

Subgroup analysis and investigation of heterogeneity

When sufficient data were available, we conducted subgroup analyses to identify separate evidence within the following subgroups.

- Type, extent and severity of the uterine abnormality treated.

We aimed to report the interpretation of any subgroup analysis conservatively, even if sufficient data were available; subgroup analysis is observational in nature and can be helpful in generating or exploring hypotheses. Moreover, valid interpretation of statistical tests to detect differences between subgroups is not without problems.

Sensitivity analysis

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

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

Studies that reported both live birth and clinical pregnancy rates were assessed for overestimation of the effect size

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

We generated a 'Summary of findings' table for the key outcomes of live birth and presence of IUAs at second-look hysteroscopy using GRADEPRO software (version 3.2.2.20090501) (http://ims.cochrane.org/gradepro). This table presents details of the overall quality of the body of evidence for these two key outcomes based on GRADE (Grades of Recommendation, Assessment, Development and Evaluation) criteria (i.e. study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias). We justified, documented and incorporated judgements about evidence quality (high, moderate or low) into reporting of results for each outcome.

RESULTS

Description of studies

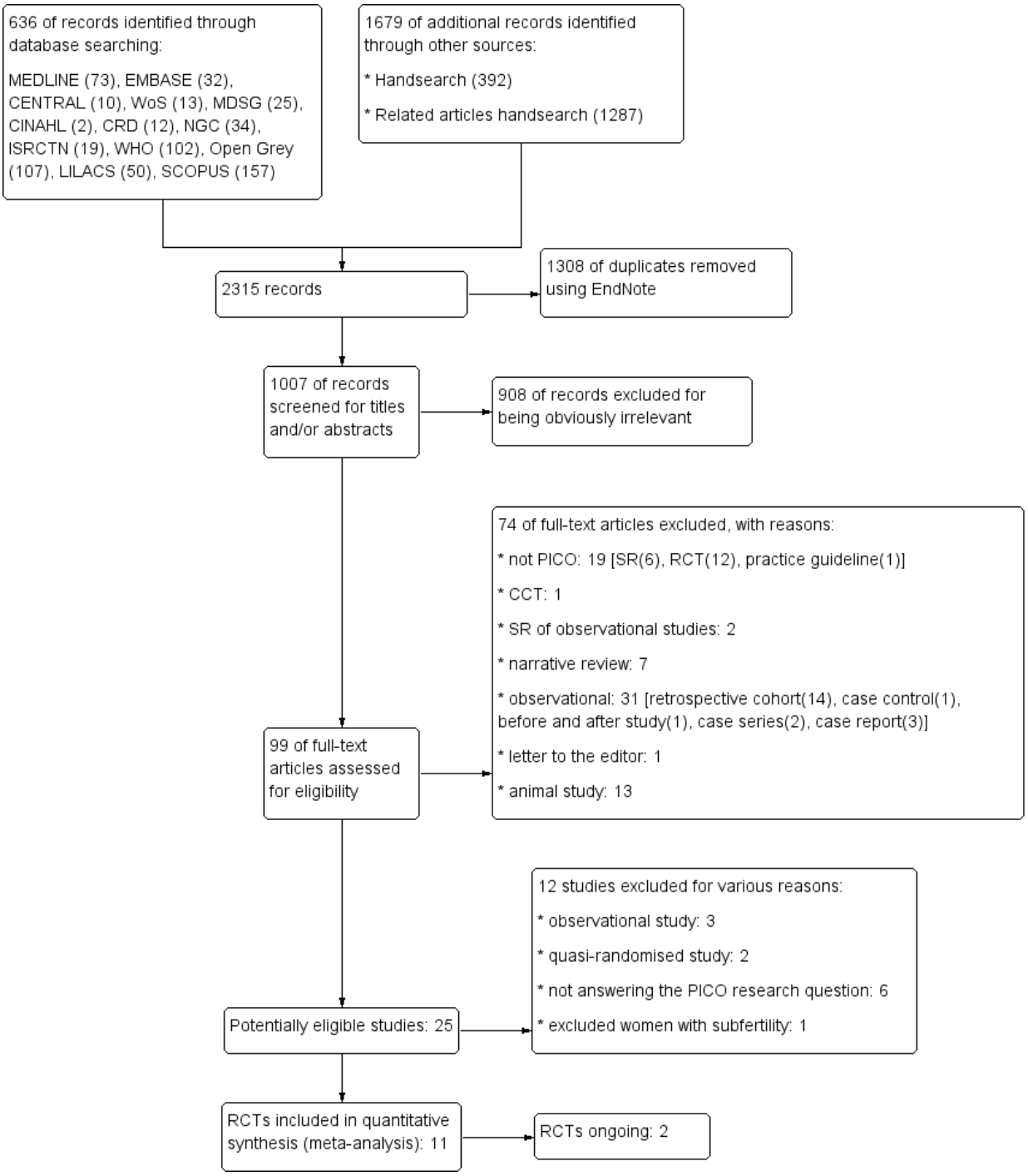
See Characteristics of included studies, Characteristics of excluded studies, Characteristics of studies awaiting classification and Characteristics of ongoing studies.

Results of the search

We identified 636 records by searching the following databases: CENTRAL (10), MDSG Specialised Register (25), MEDLINE (73), EMBASE (32), WoS (13), CINAHL (2), CDSR (12), National Guideline Clearinghouse (34), ISRCTN Register of Controlled Trials (19) and WHO ICTRP (102), LILACS (50), Open Grey (107) and Scopus (157). We retrieved 1679 additional records through other sources: handsearch of *The Journal of Minimally Invasive Gynecology* (392) and handsearch of related articles on included studies (1287).

After combining 636 records identified through electronic searches with 1679 additional records obtained by searching other sources, we screened 2315 records for duplicates by using specialised software (https://www.myendnoteweb.com): We removed 1308 duplicates. We screened 1007 records for titles and abstracts and excluded 908 records for being obviously irrelevant. We assessed 99 full-text articles for eligibility and identified 25 potentially eligible studies. We excluded 12 studies for various reasons (Characteristics of excluded studies). We included 11 studies in the present Cochrane review for quantitative synthesis and critical appraisal (Characteristics of included studies); two trials are ongoing (Characteristics of ongoing studies).
See the PRISMA flow chart (Figure 1).

Figure 1. Study flow diagram.



Included studies

Study design and setting

We included 11 parallel-design RCTs: 10 studies used two comparison groups (Abu Rafea 2013; Acunzo 2003; Dabir-Ashrafi 1996; De Iaco 2003; Di Spiezio Sardo 2011; Fuchs 2014; Guida 2004; Lin 2013; Lin 2015; Roy 2014), and one study (Amer 2010) used three comparison groups. All were single-centre studies: five from Italy (Acunzo 2003; De Iaco 2003; Guida 2004; Di Spiezio Sardo 2011; Guida 2004), one from Egypt (Amer 2010), one from Saudi Arabia (Abu Rafea 2013), one from Iran (Dabir-Ashrafi 1996), one from India (Roy 2014), one from Taiwan (Lin 2015) and one from China (Lin 2013).

Funding sources

See Characteristics of included studies.

In six of 11 studies, primary authors stated that they had obtained no external funding and declared no potential conflicts of interest (Amer 2010; De Iaco 2003; Di Spiezio Sardo 2011; Fuchs 2014; Guida 2004; Roy 2014). In four of 11 studies, external funding and other potential conflicts of interest are unclear; we failed to obtain clarification from corresponding authors of the primary study report despite several queries (Abu Rafea 2013; Acunzo 2003; Dabir-Ashrafi 1996; Lin 2015). One study (Lin 2013) reported external funding provided by the Chinese Government.

Participants

See Characteristics of included studies.

Abu Rafea 2013 randomly assigned 28 women suffering from infertility and/or adverse pregnancy outcomes diagnosed with an intrauterine septum by hysterosalpingography (HSG), sonohysterography and/or hysteroscopy. Mean participant age was 29 years (range 23 to 38 years) in the intervention group and 32 years (range 22 to 40 years) in the control group. Three subfertile women were included in the intervention group, and two in the control group.

Acunzo 2003 included 92 women with irregular menses and IUAs. Mean age (SD) of participants was 30.1 years (SD 3.5 years). Subfertile women numbered 18 in the intervention group and 16 in the control group.

Amer 2010 included 45 women with severe IUAs - all suffering from subfertility. Median participant age was 30.4 years (range 26 to 40 years).

Dabir-Ashrafi 1996 recruited 59 study participants with subfertility (15 women) and recurrent miscarriage (44 women) with a fundal defect on HSG. Participants were 26.7 ± 6.5 years of age in the intervention group and 28.4 ± 4.5 years of age in the control group.

De Iaco 2003 included 60 women 18 to 65 years of age: Women were eligible for inclusion if they were undergoing endometrial ablation or hysteroscopic removal of submucosal fibroids, endometrial polyps, septate uterus or intrauterine synechiae. The study report does not mention whether the women suffered from infertility and, if so, how many.

Di Spiezio Sardo 2011 included 110 women diagnosed at office diagnostic hysteroscopy with single or multiple lesions suitable for surgical treatment or with resistant dysfunctional uterine bleeding requiring endometrial ablation. Mean participant age (SD) was 37 years (SD 3.1 years) in the intervention group and 36 years (SD 2.9 years) in the control group. The number of subfertile women was limited: 12 were reported in the intervention group and nine in the control group.

Fuchs 2014 included 52 women who underwent hysteroscopic surgery because of suspected retained products of conception. Mean participant age (SD) was 29.5 years (SD 5.1 years) in the intervention group and 31.4 years (SD 6.5 years) in the control group. This study included only women with proven fertility.

Guida 2004 included 138 women with surgically treatable single lesions (fibroids, polyps and uterine septa, subgroups I to III) at diagnostic hysteroscopy. Mean participant age (SD) was 37 years (SD 3.2 years) in the intervention group and 36 years (SD 2.8 years) in the control group. Numbers of subfertile women and their individual outcome data were not available for further analysis.

Lin 2013 is a single-centre study including 201 women with hysteroscopically confirmed IUAs of moderate or severe degree (American Fertility Society (AFS) score range $\geq$ 5). Age, parity, menstrual characteristics and AFS score before surgery were comparable between groups. Proportions of subfertile women were 26% in the balloon group and 22% in the IUD groups.

Lin 2015 included 62 women 20 to 45 years of age undergoing hysteroscopy. Mean participant age (SD) was 33 years (SD 4.8 years) in the intervention group and 35 years (SD 7.2 years) in the control group. The number of participants who suffered from subfertility is not provided.

Roy 2014 included 90 women with septate uterus with a history of miscarriage or subfertility. Mean participant age (SD) was 28.7 years (4.8 years) in the intervention group and 27.3 years (SD 3.9 years) in the control group. Mean duration of subfertility (SD) was 5.9 years (SD 1.8 years) in the intervention group and 6.2 years (SD 1.1 years) in the control group.

Interventions and comparators

See Characteristics of included studies.

- Inserted balloon stent versus no treatment (Abu Rafea 2013; Lin 2015).
- Inserted IUD copper coil versus specially designed intrauterine (IU) balloon (Lin 2013).
- Hormonal treatment versus no treatment or placebo (Dabir-Ashrafi 1996; Roy 2014).
- Barrier gel versus no treatment (Acunzo 2003; De Iaco 2003; Di Spiezio Sardo 2011; Fuchs 2014; Guida 2004).
- Human amniotic membrane graft versus no graft (Amer 2010).

Outcomes

See Characteristics of included studies.

- Primary outcome: live birth (Abu Rafea 2013; Amer 2010; Roy 2014).
- Secondary outcomes.
  - Clinical pregnancy (Abu Rafea 2013; Amer 2010; Fuchs 2014; Roy 2014).
  - Miscarriage (Abu Rafea 2013; Amer 2010; Roy 2014).
  - Presence of IUAs at second-look hysteroscopy (Acunzo 2003; De Iaco 2003; Di Spiezio Sardo 2011; Fuchs 2014; Guida 2004; Lin 2013; Lin 2015; Roy 2014).
  - Mean adhesion scores of IUAs at second-look hysteroscopy (Acunzo 2003; Guida 2004).
  - Severity of adhesion of IUAs at second-look hysteroscopy (Acunzo 2003; De Iaco 2003; Di Spiezio Sardo 2011; Fuchs 2014; Guida 2004).

One study (Dabir-Ashrafi 1996) reported none of the outcomes prespecified for this Cochrane review.

Excluded studies

We excluded 12 studies from potentially eligible studies for the following reasons.

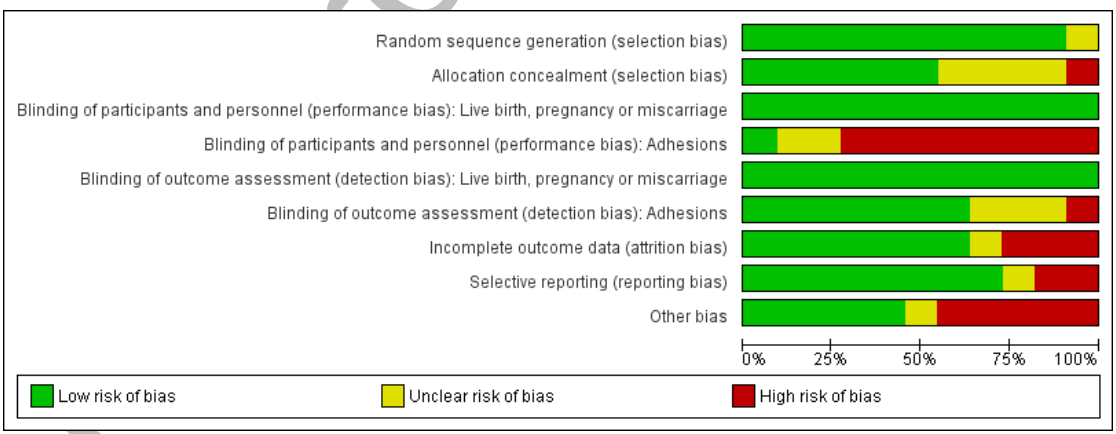
- Three of 12 were observational studies (Hu 2014a; Hu 2014b; Letouzey 2014).
- Two of 12 were quasi-randomised studies (Pabuccu 2008; Tonguc 2010).
- Six of 12 did not answer the PICO (population, intervention, comparator, outcome) research questions of the present Cochrane review (Bednarek 2011; Hooker 2011; Johns 2001; Kurtz 2002; Tsapanos 2002; Yaar 2004).
- One of 12 excluded subfertile women from participation in the trial (Kim 2012).

See Characteristics of excluded studies.

Risk of bias in included studies

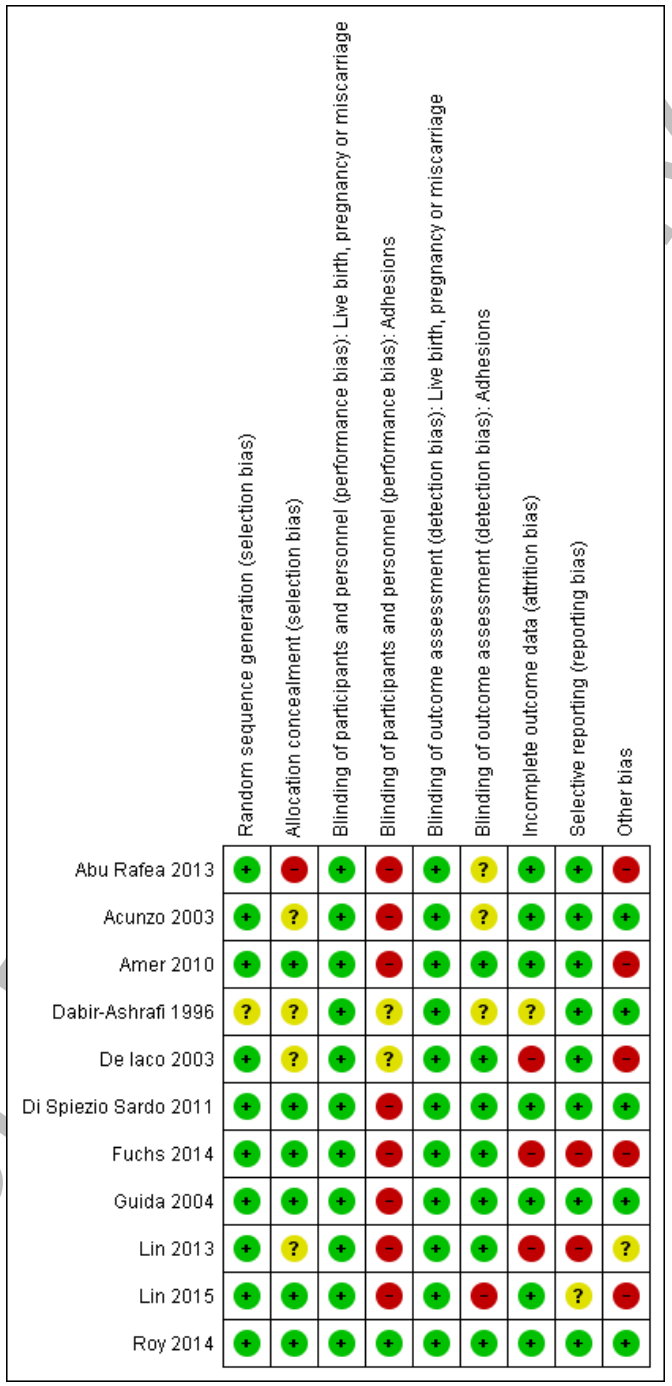
See the 'Risk of bias' summary for the review authors' judgements about each risk of bias item in the included study (Figure 2).

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



See the 'Risk of bias' graph for the review authors' judgements about each risk of bias item presented as percentages across the two included studies (Figure 3).

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



Allocation

We judged one study (Dabir-Ashrafi 1996) to be at unclear risk of selection bias in relation to random sequence generation: The study report claims that the trial is an RCT but does not describe the method of randomisation. We failed to obtain clarification from the authors of the primary study despite several mailings. We judged 10 of 11 studies to be at low risk of selection bias in relation to random sequence generation because all used computer-generated randomisation lists (Abu Rafea 2013; Acunzo 2003; Amer 2010; De Iaco 2003; Di Spiezio Sardo 2011; Fuchs 2014; Guida 2004; Lin 2013; Lin 2015; Roy 2014).

We judged one study (Abu Rafea 2013) to be at high risk of selection bias in relation to allocation concealment: Randomisation was based on a computer-generated list of numbers, but study authors did not describe allocation concealment in the primary study report. We judged four of 11 studies (Acunzo 2003; Dabir-Ashrafi 1996; De Iaco 2003; Lin 2013) to be at unclear risk of selection bias in relation to allocation concealment because study authors did not describe the method of allocation concealment and did not provide clarification as requested (Acunzo 2003; Dabir-Ashrafi 1996; Lin 2013) or provided insufficient information (De Iaco 2003). We judged six of 11 studies (Amer 2010; Di Spiezio Sardo 2011; Fuchs 2014; Guida 2004; Lin 2015; Roy 2014) to be at low risk of selection bias in relation to allocation concealment because investigators used sequentially numbered opaque sealed envelopes containing the allocated treatment (Amer 2010; Di Spiezio Sardo 2011; Fuchs 2014; Guida 2004; Lin 2015) or a code referring to the allocated treatment (Roy 2014).

Blinding

Three of 11 studies (Abu Rafea 2013; Amer 2010; Roy 2014) reported live births and four of 11 studies (Abu Rafea 2013; Amer 2010; Fuchs 2014; Roy 2014) reported clinical pregnancy as key outcomes: We judged all four studies (Abu Rafea 2013; Amer 2010; Fuchs 2014; Roy 2014) to be at low risk of performance and detection bias in relation to blinding of participants, personnel and outcome assessors because live birth and clinical pregnancy are unequivocal outcomes.

We judged eight of 11 studies (Abu Rafea 2013; Acunzo 2003; Amer 2010; Di Spiezio Sardo 2011; Fuchs 2014; Guida 2004; Lin 2013; Lin 2015) to be at high risk of performance bias in relation to blinding of participants and personnel for the outcome of presence of IUAs, as personnel (Amer 2010; Di Spiezio Sardo 2011; Fuchs 2014; Guida 2004; Lin 2013) or both participants and personnel (Abu Rafea 2013; Acunzo 2003; Lin 2015) were not blinded. We judged two studies (Dabir-Ashrafi 1996; De Iaco 2003) to be at unclear risk of performance bias in relation to blinding of participants and personnel for the key outcome of adhesions because the method of blinding of participants and personnel was not described (Dabir-Ashrafi 1996) or was not sufficiently clarified after we contacted study authors (De Iaco 2003). We judged only one of 11 studies (Roy 2014) to be at low risk of performance bias in relation to blinding of participants and personnel for the key outcome of adhesions as placebo pills were used for blinding. Lin 2015 was at high risk of detection bias in relation to blinding of outcome assessors for the outcome of adhesion formation: Outcome assessors in this trial were not blinded. We judged two of 11 studies (Abu Rafea 2013; Acunzo 2003) to be at unclear risk of detection bias in relation to blinding of outcome assessors for the key outcome of adhesion formation because the method of blinding was not reported and clarification could not be obtained from the authors of the primary study. We judged seven of 11 studies (Amer 2010; De Iaco 2003; Di Spiezio Sardo 2011; Fuchs 2014; Guida 2004; Lin 2013; Roy 2014) to be at low risk of detection bias for the key outcome of adhesions because outcome assessors were independent observers blinded to treatment allocation.

We judged one study (Dabir-Ashrafi 1996) to be at unclear risk of performance and detection bias in relation to blinding of participants, personnel and outcome assessors for a subjective outcome not prespecified in the present Cochrane review: The method was unclear, and we failed to obtain clarification.

Incomplete outcome data

We judged three of 11 studies (De Iaco 2003; Fuchs 2014; Lin 2013) to be at high risk of attrition bias. In one study (De Iaco 2003), loss to follow-up after randomisation involved 20 of 60 included participants. The second study (Fuchs 2014) excluded five of 26 participants in the intervention group and six of 26 participants in the control group after randomisation from the analysis (11/52 or 21%): Reasons for discontinuation of the trial were not clarified. Loss to follow-up in the third trial (Lin 2013) was 19%. We judged one study (Dabir-Ashrafi 1996) to be at unclear risk of attrition bias because four of 50 (8%) participants were excluded and distribution among comparison groups was not reported: We failed to obtain clarification from the study authors. We judged seven of 11 studies (Abu Rafea 2013; Acunzo 2003; Amer 2010; Di Spiezio Sardo 2011; Guida 2004; Lin 2015; Roy 2014) to be at low risk of attrition bias because all participants with relevant outcome data were included in the final data analysis (Abu Rafea 2013; Di Spiezio Sardo 2011) or loss to follow-up was small (< 10%) without imbalance across comparison groups for numbers or reasons for loss to follow-up (Acunzo 2003; Amer 2010; Guida 2004; Lin 2015; Roy 2014).

Selective reporting

We judged two of 11 studies (Fuchs 2014; Lin 2013) to be at high risk of reporting bias in relation to selective outcome reporting. One study (Fuchs 2014) failed to report data for the primary outcome of live birth despite a study duration of 27 months. A second study (Lin 2013) failed to report data for pregnancy rates in the published report of the study, although pregnancy was prespecified as a main outcome in the study protocol. We judged eight of 11 studies (Abu Rafea 2013; Acunzo 2003; Amer 2010; Dabir-Ashrafi 1996; De Iaco 2003; Di Spiezio Sardo 2011; Guida 2004; Roy 2014) to be at low risk of reporting bias in relation to selective outcome reporting. We judged one study (Lin 2015) to be at unclear risk of selective outcome reporting because we noted discrepancies between outcomes prespecified in the registered study protocol and results reported in the abstract and in the results section.

Other potential sources of bias

We judged five of 11 studies (Abu Rafea 2013; Amer 2010; De Iaco 2003; Fuchs 2014; Lin 2015) to be at high risk of other potential sources of bias. One study (Abu Rafea 2013) excluded four of 28 participants (14%) from the final analysis after randomisation because they were not trying to conceive. The reason for this post-randomisation exclusion is lack of explicit inclusion and exclusion criteria. Analysis of study results shows that poor inclusion and exclusion criteria may lead to increased risk of bias. Moreover, researchers measured outcomes in this study over 12 to 18 months: This could have affected final pregnancy results if imbalance occurred across comparison groups for the time points at which this key outcome was measured. Finally, although no statistically significant differences were evident in mean age of participants in both comparison groups, the mean difference was three years, and more younger women were included in the intervention group: This baseline imbalance between comparison groups is clinically relevant, irrespective of P values. Amer 2010 provided evidence of baseline imbalance among participant characteristics in relation to differences in the prevalence of prior cesarean section as a cause of IUAs. Moreover, investigators provided co-treatment with laparoscopy and in vitro fertilisation (IVF) for some women but reported no data on the distribution in numbers among comparison groups. De Iaco 2003 recalculated data for the outcomes of presence of IUAs at second look and severity of IUAs and reported lack of statistically significant differences between comparison groups, although study authors concluded that use of anti-adhesion barrier gel improves outcomes of hysteroscopic surgery. This conclusion is not based on available evidence. Investigators did not report baseline characteristics of both comparison groups. Fuchs 2014 at follow-up hysteroscopy offered co-treatment with hysteroscopic adhesiolysis to women with AFS II or III IUAs. They offered co-treatment to three of 20 (14%) women in the control group and to one of 21 (4%) of women in the intervention group: This may have affected the magnitude and direction of the treatment effect. Lin 2015 expressed some concern for imbalance in baseline characteristics between comparison groups: The number of participants with IUAs was twice as high in the intervention group (17/31) as in the control group (10/31).
We judged Lin 2013 to be at unclear risk of other potential sources of bias: Co-treatment consisted of repeat adhesiolysis for recurrent or de novo IUAs at second-look hysteroscopy, but the proportion of participants co-treated among comparison groups is unknown.
We judged five of 11 studies (Acunzo 2003; Dabir-Ashrafi 1996; Di Spiezio Sardo 2011; Guida 2004; Roy 2014) to be at low risk of other potential sources of bias.

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**

1. Inserted device versus no treatment

We included two studies (Abu Rafea 2013; Lin 2015).
Lin 2015 provided no data on any of the key outcomes of the present Cochrane review.
See Characteristics of included studies.

Primary outcome

1.1 Live birth or ongoing pregnancy

IUD versus no treatment

We retrieved no randomised studies for this comparison.

IU balloon versus no treatment

One study (Abu Rafea 2013) reported data for the outcome of term delivery at 12 to 18 months; we used these data as a surrogate for live birth. Investigators provided no evidence of a difference between use of an intrauterine Foley catheter balloon and no treatment following hysteroscopic septum division for the outcome of live birth (OR 1.00, 95% CI 0.18 to 5.46, P value = 1.00, one study, 24 women; Analysis 1.1).

Secondary outcomes

1.2 Clinical pregnancy

IUD versus no treatment

We retrieved no randomised studies for this comparison.

IU balloon versus no treatment

Abu Rafea 2013 did not define the outcome of pregnancy, and we failed to obtain clarification from study authors. Moreover, some women could have had more than one pregnancy during the follow-up period of 12 to 18 months - a point that could not be clarified. Researchers presented no evidence of differences between groups (OR 1.00, 95% CI 0.06 to 18.08, P value = 1.00, one study, 24 women; Analysis 1.2).

1.3 Miscarriage

IUD versus no treatment

We retrieved no randomised studies for this comparison.

IU balloon versus no treatment

Abu Rafea 2013 reported this outcome. Some individual women could have had more than one miscarriage during the follow-up period of 12 to 18 months; we failed to clarify this with study authors despite frequent mailings with open-ended queries. Study authors provided no evidence of differences between groups (OR 0.66, 95% CI 0.11 to 4.00, P value = 0.65, one study, 22 pregnancies in 24 women; Analysis 1.3).

1.4 Presence of intrauterine adhesions at second-look hysteroscopy

IUD versus no treatment

We retrieved no randomised studies for this comparison.

IU balloon versus no treatment

One study (Lin 2015) reported that the effect of inserting an IU balloon stent for decreasing IUAs compared with no treatment following operative hysteroscopy was undetermined because neither arm reported events (OR not estimable, one study, 60 women; Analysis 1.4).

This study did not report our other secondary outcomes.

Subgroup analyses

We conducted no subgroup analyses.

Sensitivity analyses

In Abu Rafea 2013, some women (4/28, or 14% of participants) were not trying to conceive after treatment, although they had been randomly assigned (1/13 in the intervention group and 3/15 in the control group). As prespecified in the protocol under Dealing with missing data, we conducted a sensitivity analysis (Analysis 1.1) on the choice to use an available data analysis rather than an intention-to-treat analysis (ITT) with the imputation that no live births would have occurred in women without a reported outcome. The ITT yielded no evidence of differences between groups (OR 1.40, 95% CI 0.31 to 6.33, P value = 0.66, one study, 28 women, ITT analysis).

2. Inserted device versus another inserted device

We included one study (Lin 2013).

See Characteristics of included studies.

Primary outcome

2.1 Live birth or ongoing pregnancy

We retrieved no randomised studies reporting this outcome.

Secondary outcomes

2.2 Clinical pregnancy

We retrieved no randomised studies reporting this outcome.

2.3 Miscarriage

We retrieved no randomised studies reporting this outcome.

2.4 Presence of intrauterine adhesions at second-look hysteroscopy

We found no evidence of differences between comparison groups (OR 1.23, 95% CI 0.64 to 2.37, P value = 0.54, one study, 162 women; Analysis 2.1).

We found no reports on our other secondary outcomes.

Subgroup analyses

We conducted no subgroup analyses.

Sensitivity analyses

We conducted no sensitivity analyses.

3. Hormonal treatment versus no treatment or placebo

We retrieved two studies (Dabir-Ashrafi 1996; Roy 2014). Dabir-Ashrafi 1996 provided no data on any of the key outcomes of the present Cochrane review.
See Characteristics of included studies.

Primary outcome

3.1 Live birth or ongoing pregnancy

Hormonal treatment versus no treatment

We retrieved no randomised studies reporting this outcome.

Hormonal treatment versus placebo

We considered the outcome of ongoing pregnancy reported in Roy 2014 as a surrogate for live birth. We found no evidence of differences between groups (OR 0.93, 95% CI 0.37 to 2.33, P value = 0.87, one study, 83 women; Analysis 3.1).

Secondary outcomes

3.2 Clinical pregnancy

Hormonal treatment versus no treatment

We retrieved no randomised studies reporting this outcome.

Hormonal treatment versus placebo

We found no evidence of differences between groups (OR 0.85, 95% CI 0.35 to 2.06, P value = 0.72, one study, 83 women; Analysis 3.2).

3.3 Miscarriage

Hormonal treatment versus no treatment

We found no data for this secondary outcome.

Hormonal treatment versus placebo

We found no evidence of differences between groups (OR 0.72, 95% CI 0.10 to 5.01, P value = 0.74, one study, 32 pregnancies in 83 women; Analysis 3.3).

3.4 Presence of intrauterine adhesions at second-look hysteroscopy

Hormonal treatment versus no treatment

We found no data for this outcome.

Hormonal treatment versus placebo

We found no evidence of differences between groups (OR 0.14, 95% CI 0.01 to 2.72, P value = 0.19, one study, 85 women; Analysis 3.4).
We found no report of our other secondary outcomes.
Subgroup analyses
We conducted no subgroup analyses.
Sensitivity analyses
We conducted no sensitivity analyses.

4. Gel versus no treatment

4.1 HA gel versus no treatment

We included three single-centre studies from Italy (Acunzo 2003; De Iaco 2003; Guida 2004).
See Characteristics of included studies.

Primary outcome

4.1.1 Live birth or ongoing pregnancy

We retrieved no randomised studies reporting this outcome.

Secondary outcomes

4.1.2 Clinical pregnancy

We retrieved no randomised studies reporting this outcome.

4.1.3 Miscarriage

We retrieved no randomised studies reporting this outcome.

4.1.4 Presence of intrauterine adhesions at second-look hysteroscopy

Pooled analysis of the findings of Acunzo 2003, De Iaco 2003 and Guida 2004 indicates that use of HA gel is associated with fewer IUAs at second-look hysteroscopy at nine to 12 weeks following operative hysteroscopy compared with no treatment (OR 0.41, 95% CI 0.22 to 0.77, P value = 0.006, three studies, 256 women; Analysis 4.2). We found no statistical evidence of heterogeneity (Chi^2 = 1.29, df = 2 (P value = 0.53), I^2 = 0%).

The number needed to treat for an additional beneficial outcome (NNTB) is 7 (95% CI 4 to 20).

Subgroup analysis

We conducted a subgroup analysis based on the results of Acunzo 2003 and Guida 2004 according to the type of pathology treated by operative hysteroscopy.

Subgroup analysis revealed no evidence of differences between arms with use of HA gel following operative hysteroscopy for fibroids (OR 0.38, 95% CI 0.10 to 1.49, P value = 0.17, one study, 49 women), endometrial polyps (OR 0.28, 95% CI 0.05 to 1.51, P value = 0.14, one study, 67 women), uterine septa (OR 0.24, 95% CI 0.02 to 3.01, P value = 0.27, one study, 16 women) nor IUAs (OR 0.35, 95% CI 0.12 to 1.03, P value = 0.06, one study, 84 women). Presumably this was due to loss of power, as the point estimates were consistently in favour of treatment with the barrier gel. We found no evidence of substantial subgroup differences (Chi^2 = 0.15, df = 3 (P value = 0.99), I^2 = 0%).

Data from this subgroup analysis should be treated with caution and should not be overinterpreted, as subgroup analysis by itself is observational in nature, and statistical interpretation of results is not without problems.

4.1.5 Mean adhesion scores at second-look hysteroscopy

Pooled analysis of the findings of Acunzo 2003 and Guida 2004 revealed a statistically significantly lower mean adhesion score at second-look hysteroscopy at 12 weeks in women treated by operative hysteroscopy for any intrauterine pathology after use of HA gel compared with no treatment (MD -1.90, 95% CI -3.21 to -0.59, P value = 0.005, two studies, 43 women). Statistical heterogeneity beyond chance was high (Chi^2 = 77.43, df = 3 (P value < 0.00001), I^2 = 96.1%; Analysis 4.3). When considering the studies separately, we found no statistical heterogeneity in the findings of Guida 2004 (women treated for any uterine pathology except IUAs) and Acunzo 2003 (women treated for IUAs). Researchers reported a decrease in mean adhesion scores among women treated for any uterine pathology, except IUAs, at -1.44 (95% CI -1.83 to -1.05, P value < 0.00001, one study, 24 women) (Chi^2 = 0.24, df = 2 (P value = 0.88), I^2 = 0%).

Subgroup analysis

Subgroup analysis showed that use of HA gel following operative hysteroscopy for fibroids (MD -1.25, 95% CI -2.21 to -0.29, P value = 0.01, one study, 12 women), endometrial polyps (MD -1.50, 95% CI -1.95 to -1.05, P value < 0.00001, one study, eight women), uterine septa (MD -1.33, 95% CI -2.65 to -0.01, P value = 0.05, one study, four women) or IUAs (MD -3.30, 95% CI -3.43 to -3.17, P value < 0.00001, one study, 19 women) was associated with a consistent decrease in mean adhesion AFS 1988 score at second-look hysteroscopy at 12 weeks; differences between subgroups for this randomised comparison were high beyond chance (Chi^2 = 77.43, df = 3 (P value < 0.00001); I^2 = 96.1%; Analysis 4.3). Separate consideration of the findings of Guida 2004 (women treated for any uterine pathology except IUAs) and Acunzo 2003 (women treated for IUAs) revealed no statistical heterogeneity.

4.1.6 Severity of adhesions at second-look laparoscopy

Mild adhesions at second-look hysteroscopy

Pooled analysis of the findings of Acunzo 2003, De Iaco 2003 and Guida 2004 revealed that use of HA gel in women treated by operative hysteroscopy for any intrauterine pathology is associated with more mild adhesions at second-look hysteroscopy at nine to 12 weeks compared with no treatment (OR 18.66, 95% CI 3.92 to 88.90, P value = 0.0002, three studies, 55 women) and showed no statistical heterogeneity (Chi^2 = 0.42, df = 2 (P value = 0.81), I^2 = 0%; Analysis 4.4).

The NNTB is 1 (95% CI 1 to 2).

Moderate or severe adhesions at second-look hysteroscopy

Pooled analysis of the findings of Acunzo 2003, De Iaco 2003 and Guida 2004 showed that use of HA gel in women treated by operative hysteroscopy for any intrauterine pathology is associated with a lower proportion of moderate or severe adhesions at second-look hysteroscopy at nine to 12 weeks compared with no treatment (OR 0.05, 95% CI 0.01 to 0.26, P value = 0.0002, three studies, 55 women) and revealed no statistical heterogeneity (Chi^2 = 0.42, df = 2 (P value = 0.81), I^2 = 0%; Analysis 4.5).

The NNTB is 1 (95% CI 1 to 2).

Sensitivity analyses

We did not conduct sensitivity analyses to investigate the impact of study quality on the direction or magnitude of effect size because all included studies had at least one item at high risk of bias for one domain. We did not study the impact of missing outcome data or alternative imputation strategies on results of the meta-analysis because data for the primary outcome of live birth were lacking. Multiple sensitivity analyses demonstrated that results of pooled analyses were independent of the choice of analysis model and the summary effect measure.

4.2 Poly gel versus no treatment

Primary outcome

4.2.1 Live birth or ongoing pregnancy

We retrieved no randomised studies reporting this outcome.

Secondary outcomes

4.2.2 Clinical pregnancy

Fuchs 2014 provided no evidence of differences between groups (OR 2.83, 95% CI 0.62 to 13.04, P value = 0.18, one study, 41 women; Analysis 4.1).

4.2.3 Miscarriage

We retrieved no randomised studies reporting this outcome.

4.2.4 Presence of intrauterine adhesions at second-look hysteroscopy

Di Spiezio Sardo 2011 provided no evidence of differences between groups at zero to four weeks (OR 0.19, 95% CI 0.03 to 1.27, P value = 0.09, one study, 86 women; Analysis 4.2).

Fuchs 2014 provided no evidence of differences between groups at five to eight weeks (OR 0.28, 95% CI 0.03 to 2.98, P value = 0.29, one study, 41 women; Analysis 4.2).

Subgroup analyses

Limited data from Di Spiezio Sardo 2011 allowed us to conduct one subgroup analysis according to the type of pathology treated by operative hysteroscopy. Analysis yielded no evidence of differences between arms for use of poly gel following operative hysteroscopy for fibroids (OR 0.27, 95% CI 0.02 to 2.90, P value = 0.28, one study, 31 women), endometrial polyps (OR not estimable because both comparison groups reported no events, one study, 42 women) and uterine septa (OR 0.10, 95% CI 0.00 to 2.42, P value = 0.16, one study, 13 women) compared with no treatment. This was believed to be due to loss of power, as point estimates consistently favoured treatment with the barrier gel. We found no evidence of substantial subgroup differences (Chi^2 = 0.24, df = 1 (P value = 0.63), I^2 = 0%).

Data from this subgroup analysis should be treated with caution and should not be over-interpreted, as subgroup analysis by itself is observational in nature, and statistical interpretation of results is not without problems.

4.2.5 Mean adhesion scores at second-look laparoscopy

We retrieved no randomised studies reporting this outcome.

4.2.6 Severity of adhesions at second-look laparoscopy

Mild adhesions at second-look hysteroscopy

Di Spiezio Sardo 2011 provided no evidence of differences between groups at zero to four weeks (OR 11.00, 95% CI 0.28 to 433.80, P value = 0.20, one study, seven women; Analysis 4.4).

Moderate or severe adhesions at second-look hysteroscopy

Di Spiezio Sardo 2011 provided no evidence of differences between groups at zero to four weeks (OR 0.09, 95% CI 0.00 to 3.59, P value = 0.20, one study, seven women; Analysis 4.5).

Fuchs 2014 provided evidence of differences between groups at five to eight weeks (OR 0.28, 95% CI 0.03 to 2.98, P value = 0.29, one study, 41 women; Analysis 4.5).

Sensitivity analyses

We excluded from further analysis the data from 24 participants in Di Spiezio Sardo 2011 who underwent endometrial ablation, as endometrial ablation/resection is not a fertility-enhancing intervention. We subjected this decision to a sensitivity analysis. We found no substantial impact on effect size or on tests of statistical significance when we considered the results of all participants from Di Spiezio Sardo 2011 (OR 0.36, 95% CI 0.20 to 0.62, P value = 0.0003, five studies, 407 women) versus data from 24 women treated by endometrial ablation who were excluded for Analysis 4.2 (OR 0.37, 95% CI 0.20 to 0.67, P value = 0.0010, five studies, 383 women).

We performed no sensitivity analyses to investigate impact of study quality on the direction or magnitude of effect size because all included studies had at least one item at high risk of bias for one domain. We did not study the impact of missing outcome data or alternative imputation strategies on results of the meta-analysis, as data for the primary outcome of live birth were lacking.

Multiple sensitivity analyses showed that results of pooled analyses were independent of the choice of analysis model and of the summary effect measure.

4.3 HA or poly gel versus no treatment

Primary outcome

4.3.1 Live birth or ongoing pregnancy

We retrieved no randomised studies reporting this outcome.

Secondary outcomes

4.3.2 Clinical pregnancy

Fuchs 2014 provided no evidence of differences between groups (OR 2.83, 95% CI 0.62 to 13.04, P value = 0.18, one study, 41 women; Analysis 4.1).

4.3.3 Miscarriage

We retrieved no randomised studies reporting this outcome.

4.3.4 Presence of intrauterine adhesions at second-look hysteroscopy

Pooled analysis of the findings of Acunzo 2003, De Iaco 2003, Di Spiezio Sardo 2011, Fuchs 2014 and Guida 2004 revealed an association between use of HA or poly gel versus no treatment and fewer IUAs at any second-look hysteroscopy following operative hysteroscopy (OR 0.37, 95% CI 0.20 to 0.67, P value = 0.0010, five studies, 383 women; Analysis 4.2) and showed no statistical heterogeneity (Chi^2 = 2.23, df = 4 (P value = 0.69), I^2 = 0%). The NNTB is 8 (95% CI 5 to 17).

Subgroup analyses

Subgroup analysis of Analysis 4.2, according to type of gel and timing of the second-look hysteroscopy, revealed differences between arms for use of HA gel at second-look hysteroscopy at nine to 12 weeks (OR 0.41, 95% CI 0.22 to 0.77, 256 participants, three studies, I^2 = 0%) but not for poly gel at zero to four weeks (OR 0.14, 95% CI 0.02 to 1.21, 86 participants, one study, I^2 = 0%) nor for poly gel at five to eight weeks (OR 0.28, 95% CI 0.03 to 2.98, 41 participants, one study, I^2 = 0%) compared with no treatment. We found no subgroup differences (Chi^2 = 0.93, df = 2 (P value = 0.63), I^2 = 0%; Analysis 4.2). This was believed to be due to loss of power.

Data from this subgroup analysis should be treated with caution and should not be over-interpreted, as subgroup analysis by itself is observational in nature, and statistical interpretation of results is not without problems. Moreover, this subgroup analysis according to type of gel and timing of the second-look procedure, although it made clinical sense, was a post hoc analysis.

Mean adhesion scores at second-look hysteroscopy

Pooled analysis of the findings of Acunzo 2003 and Guida 2004 revealed a statistically significantly lower mean adhesion score at second-look hysteroscopy at 12 weeks in women treated by operative hysteroscopy for any intrauterine pathology after use of gel compared with no treatment (MD -1.90, 95% CI -3.21 to -0.59, P value = 0.005, two studies, 43 women). Statistical heterogeneity beyond chance was high (Chi^2 = 77.43, df = 3 (P value < 0.00001); I^2 = 96.1%; Analysis 4.3). Separate consideration of the findings of Guida 2004 (women treated for any uterine pathology except IUAs) and Acunzo 2003 (women treated for IUAs) showed no statistical heterogeneity. Researchers reported a decrease in mean adhesion score of -1.44 among women treated for any uterine pathology except IUAs (95% CI -1.83 to -1.05, P value < 0.00001, one study, 24 women; Chi^2 = 0.24, df = 2 (P value = 0.88), I^2 = 0%).

Subgroup analyses

Use of any gel following operative hysteroscopy for fibroids (MD -1.25, 95% CI -2.21 to -0.29, P value = 0.01, one study, 12 women), endometrial polyps (MD -1.50, 95% CI -1.95 to -1.05, P value < 0.00001, one study, eight women), uterine septa (MD -1.33, 95% CI -2.65 to -0.01, P value = 0.05, one study, four women) and IUAs (MD -3.30, 95% CI -3.43 to -3.17, P value < 0.00001, one study, 19 women) is consistently associated with lower mean adhesion scores at second-look hysteroscopy; differences between subgroups for this randomised comparison were high beyond chance (Chi^2 = 77.43, df = 3 (P value < 0.00001), I^2 = 96.1%; Analysis 4.3). Separate consideration of the findings of Guida 2004 (women treated for any uterine pathology except IUAs) and Acunzo 2003 (women treated for IUAs) showed no statistical heterogeneity.

Data from this subgroup analysis should be treated with caution and should not be over-interpreted, as subgroup analysis by itself is observational in nature, and statistical interpretation of results is not without problems.

4.3.5 Severity of adhesions at second-look laparoscopy

Mild adhesions at second-look hysteroscopy

Pooled analysis of the findings of Acunzo 2003, De Iaco 2003, Di Spiezio Sardo 2011 and Guida 2004 revealed that use of HA or poly gel in women treated by operative hysteroscopy for any intrauterine pathology is associated with an increased proportion of mild adhesions at any second-look hysteroscopy compared with no treatment (OR 17.22, 95% CI 4.09 to 72.42, P value = 0.0001, four studies, 62 women) and showed no statistical heterogeneity (Chi^2 = 0.49, df = 3 (P value = 0.92), I^2 = 0%; Analysis 4.4). The NNTB is 1 (95% CI 1 to 2).

Subgroup analyses

Subgroup analysis of Analysis 4.4 according to type of gel and timing of second-look hysteroscopy revealed differences between arms that favoured HA gel at second-look hysteroscopy at nine to 12 weeks (OR 18.66, 95% CI 3.92 to 88.90, 55 participants, three studies, I^2 = 0%) but not poly gel at zero to four weeks (OR 11.00, 95% CI 0.28 to 433.80, seven participants, one study, I^2 = 0%) compared with no treatment and showed no subgroup differences (Chi^2 = 0.07, df = 1 (P value = 0.80), I^2 = 0%, Analysis 4.4). This was believed to be due to loss of power.

Data from this subgroup analysis should be treated with caution and should not be over-interpreted, as subgroup analysis by itself is observational in nature, and statistical interpretation of results is not without problems. Moreover, this subgroup analysis according

to type of gel and timing of the second-look procedure, although it made clinical sense, was a post hoc analysis.

Moderate or severe adhesions at second-look hysteroscopy

Pooled analysis of the findings of Acunzo 2003, De Iaco 2003, Di Spiezio Sardo 2011, Fuchs 2014 and Guida 2004 revealed that use of HA or poly gel in women treated by operative hysteroscopy for any intrauterine pathology is associated with a decreased proportion of moderate or severe adhesions at any second-look hysteroscopy compared with no treatment (OR 0.09, 95% CI 0.03 to 0.30, P value = 0.0001, five studies, 103 women) and showed no statistical heterogeneity (Chi² = 1.75, df = 4 (P value = 0.78), I² = 0%; Analysis 4.5).

The NNTB is 2 (95% CI 1 to 5).

Subgroup analyses

Subgroup analysis of Analysis 4.5 according to type of gel and timing of second-look hysteroscopy revealed differences between arms that favoured use of HA gel at second-look hysteroscopy at nine to 12 weeks (OR 0.05, 95% CI 0.01 to 0.26, 55 participants, three studies, I^2 = 0%) but not poly gel at zero to four weeks (OR 0.09, 95% CI 0.00 to 3.59, seven participants, one study, I^2 = 0%) nor poly gel at five to eight weeks (OR 0.28, 95% CI 0.03 to 2.98, 41 participants, one study, I^2 = 0%) compared with no treatment, and showed no subgroup differences (Chi^2 = 1.34, df = 2 (P value = 0.51), I^2 = 0%; Analysis 4.5). This was believed to be due to loss of power.

Data from this subgroup analysis should be treated with caution and should not be over-interpreted, as subgroup analysis by itself is observational in nature, and statistical interpretation of results is not without problems. Moreover, this subgroup analysis, although it made clinical sense, was a post hoc analysis.

Sensitivity analyses

We excluded from further analyses data from 24 participants in Di Spiezio Sardo 2011 who underwent endometrial ablation, as endometrial ablation/resection is not a fertility-enhancing intervention. We subjected this decision to a sensitivity analysis and found no substantial impact on effect size nor on tests of statistical significance when results of all participants were taken into account (OR 0.36, 95% CI 0.20 to 0.62, P value = 0.0003, five studies, 407 women) versus data from 24 women treated by endometrial ablation who were excluded from Analysis 4.2 (OR 0.37, 95% CI 0.20 to 0.67, P value = 0.0010, five studies, 383 women).

We conducted no sensitivity analyses to investigate the impact of study quality on the direction or magnitude of effect size because all included studies had at least one item at high risk of bias for one domain. The impact of missing outcome data or alternative imputation strategies on results of the meta-analysis was not studied because data for the primary outcome of live birth were lacking.

Multiple sensitivity analyses demonstrated that results of the pooled analyses were independent of the choice of analysis model and of the summary effect measure.

5. One gel versus another gel

We retrieved no randomised studies for this comparison.

6. Graft versus no graft

We retrieved one small single-centre study from Egypt (Amer 2010).

See Characteristics of included studies.

Primary outcome

5.1 Live birth or ongoing pregnancy

This study reported data for the outcome of 'ongoing pregnancy or delivery at term'; we used this composite outcome as a surrogate for live birth. Amer 2010 provided no evidence of differences between groups (OR 1.50, 95% CI 0.14 to 15.87, P value = 0.74, one study, 43 women; Analysis 6.1).

Secondary outcomes

5.2 Clinical pregnancy

Amer 2010 provided no evidence of differences between groups (OR 2.29, 95% CI 0.42 to 12.56, P value = 0.34, one study, 43 women; Analysis 6.2).

5.3 Miscarriage

Amer 2010 provided no evidence of differences between groups (OR 1.67, 95% CI 0.07 to 37.73, P value = 0.75, 10 pregnancies in 43 women; Analysis 6.3).

Studies did not report our other secondary outcomes.

Subgroup analyses

We conducted no subgroup analyses.

Sensitivity analyses

We conducted no sensitivity analyses.

6. Any therapy versus no treatment or placebo

We included nine studies for this randomised comparison (Abu Rafea 2013; Acunzo 2003; Amer 2010; De Iaco 2003; Di Spiezio Sardo 2011; Fuchs 2014; Guida 2004; Lin 2015; Roy 2014).

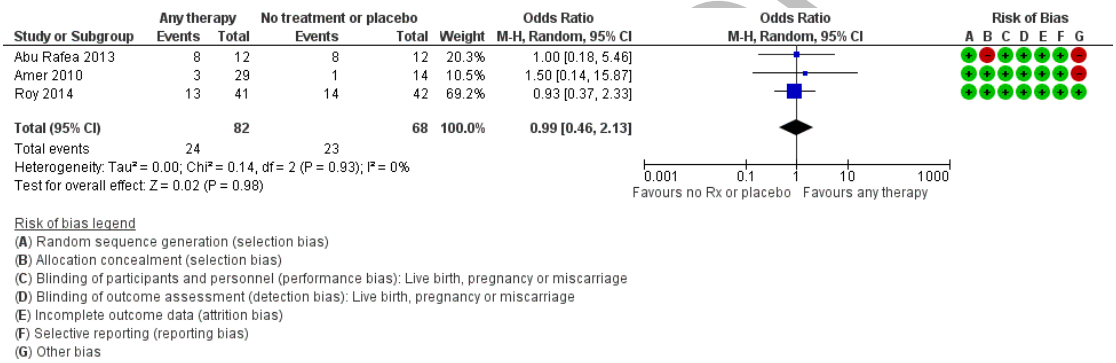
See Characteristics of included studies.

Primary outcome

6.1 Live birth or ongoing pregnancy

Pooled analysis of the findings of Abu Rafea 2013, Amer 2010 and Roy 2014 revealed no evidence of differences between groups (OR 0.99, 95% CI 0.46 to 2.13, P value = 0.98, three studies, 150 women; Analysis 7.1; Figure 4) and no statistical heterogeneity (Chi^2 = 0.14, df = 2 (P value = 0.93), I^2 = 0%).

Figure 4. Forest plot of comparison: 7 Any therapy vs no treatment or placebo, outcome: 7.1 Live birth.



Secondary outcomes

6.2 Clinical pregnancy

Pooled analysis of data from Abu Rafea 2013, Amer 2010, Fuchs 2014 and Roy 2014 revealed no evidence of differences between groups (OR 1.27, 95% CI 0.65 to 2.51, P value = 0.49, four studies, 191 women) and no statistical heterogeneity (Chi^2 = 2.35, df = 3 (P value = 0.50), I^2 = 0%; Analysis 7.2).

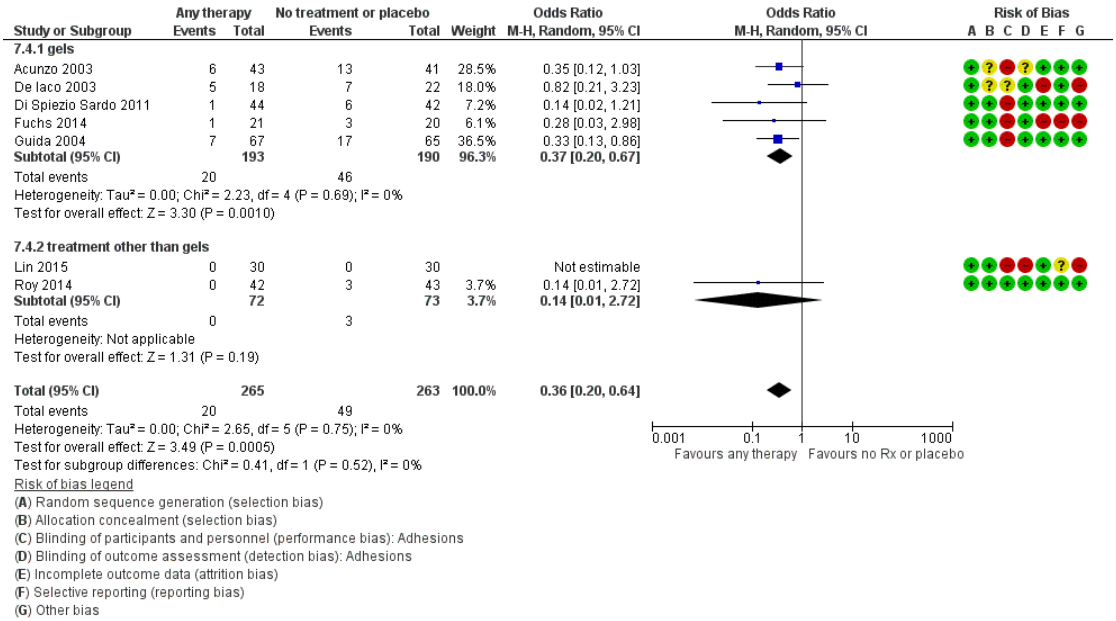
6.3 Miscarriage

Pooled analysis of findings from Abu Rafea 2013, Amer 2010 and Roy 2014 revealed no evidence of differences between groups (OR 0.78, 95% CI 0.23 to 2.65, P value = 0.70, three studies, 64 pregnancies in 150 women) and no statistical heterogeneity (Chi ^{2} = 0.27, df = 2 (P value = 0.87), I^2 = 0%; Analysis 7.3).

6.4 Presence of intrauterine adhesions at second-look hysteroscopy

Pooled analysis of findings from Acunzo 2003, De Iaco 2003, Di Spiezio Sardo 2011, Fuchs 2014, Guida 2004, Lin 2015 and Roy 2014 revealed that use of any anti-adhesion therapy versus no treatment or placebo following operative hysteroscopy is associated with fewer IUAs at any second-look hysteroscopy (OR 0.36, 95% CI 0.20 to 0.64, P value = 0.0005, seven studies, 528 women) and showed no statistical heterogeneity (Chi^2 = 2.65, df = 5 (P value = 0.75), I^2 = 0%; Analysis 7.4; Figure 5).

Figure 5. Forest plot of comparison: 7 Any therapy vs no treatment or placebo, outcome: 7.4 Presence of intrauterine adhesions at second-look hysteroscopy.



The NNTB is 9 (95% CI 6 to 20).

Studies did not report our other secondary outcomes.

Subgroup analyses

Subgroup analysis of Analysis 7.4 according to type of anti-adhesion treatment revealed differences between comparison groups for use of gels (OR 0.37, 95% CI 0.20 to 0.67, 383 participants, five studies, I^2 = 0%) but not for treatment other than gels (OR 0.14, 95% CI 0.01 to 2.72, 145 participants, two studies, I^2 = 0%) compared with no treatment for the outcome of IUAs present at any second-look hysteroscopy and showed no subgroup differences (Chi^2 = 0.41, df = 1 (P value = 0.52), I^2 = 0%; Analysis 7.4). Data from this subgroup analysis should be treated with caution and should not be over-interpreted, as subgroup analysis by itself is observational in nature, and statistical interpretation of results is not without problems. Moreover, this subgroup analysis according to type of treatment, although it made clinical sense, was a post hoc analysis.

6.5 Mean adhesion scores at second-look laparoscopy

Pooled analysis of findings from Acunzo 2003 and Guida 2004 revealed that use of any therapy versus no treatment or placebo is associated with lower mean adhesion scores at second-look hysteroscopy (MD -1.90, 95% CI -3.21 to -0.59, P value = 0.005, two studies, 43 women). Statistical heterogeneity beyond chance was high (Chi^2 = 77.43, df = 3 (P value < 0.00001), I^2 = 96%; Analysis 7.5). Separate consideration of the findings of Guida 2004 (women treated for any uterine pathology except IUAs) and Acunzo 2003 (women treated for IUAs) revealed no statistical heterogeneity.

Subgroup analyses

Subgroup analysis of Analysis 7.5 according to type of pathology treated use of any gel following operative hysteroscopy for fibroids (MD -1.25, 95% CI -2.21 to -0.29, P=0.01, 1 study, 12 women), endometrial polyps (MD -1.50, 95% CI -1.95 to -1.05, P<0.00001, 1 study, 8 women), uterine septa (MD -1.33, 95% CI -2.65 to -0.01, P=0.05, 1 study, 4 women) or IUAs (MD -3.30, 95% CI -3.43 to -3.17, P<0.00001, 1 study, 19 women) is consistently associated with lower mean adhesion scores at second-look hysteroscopy; differences between subgroups for this randomised comparison were high beyond chance (Chi^2 = 77.43, df = 3 (P value < 0.00001), I^2 = 96.1%; Analysis 7.5). Separate consideration of the findings of Guida 2004 (women treated for any uterine pathology except IUAs) and Acunzo 2003 (women treated for IUAs) revealed no statistical heterogeneity.

Data from this subgroup analysis should be treated with caution and should not be over-interpreted, as subgroup analysis by itself is observational in nature, and statistical interpretation of results is not without problems.

6.6 Severity of adhesions at second-look laparoscopy

Mild adhesions at second-look hysteroscopy

Pooled analysis of the findings of Acunzo 2003, De Iaco 2003, Di Spiezio Sardo 2011 and Guida 2004 revealed that use of any therapy compared with no treatment or placebo is associated with an increase in the proportion of mild adhesions at any second-look hysteroscopy compared with no treatment (OR 17.22, 95% CI 4.09 to 72.42, P value = 0.0001, four studies, 62 women) and showed no statistical heterogeneity (Chi² = 0.49, df = 3 (P value = 0.92), I² = 0%; Analysis 7.6).

The NNTB was 1 (95% CI 1 to 2).

Subgroup analyses

Subgroup analysis of Analysis 7.6 according to type of gel and timing of second-look hysteroscopy revealed differences between comparison groups that favoured HA gel at second-look hysteroscopy at nine to 12 weeks (OR 18.66, 95% CI 3.92 to 88.90, 55 participants, three studies, I^2 = 0%) but not poly gel at zero to four weeks (OR 11.00, 95% CI 0.28 to 433.80, seven participants, one study, I^2 = 0%) versus no treatment for this outcome and showed no subgroup differences (Chi² = 0.07, df = 1 (P value = 0.80), I² = 0%; Analysis 7.6).

Data from this subgroup analysis should be treated with caution and should not be over-interpreted, as subgroup analysis by itself is observational in nature, and statistical interpretation of results is not without problems. Moreover, this subgroup analysis, although it made clinical sense, was a post hoc analysis.

Moderate or severe adhesions at second-look hysteroscopy

Pooled analysis of the findings of Acunzo 2003, De Iaco 2003, Di Spiezio Sardo 2011, Fuchs 2014 and Guida 2004 revealed that use of any therapy versus no treatment or placebo was associated with a decrease in the proportion of moderate or severe adhesions at any second-look hysteroscopy compared with no treatment (OR 0.09, 95% CI 0.03 to 0.30, P value = 0.0001, five studies, 103 women) and showed no statistical heterogeneity (Chi² = 1.75, df = 4 (P value = 0.78), I² = 0%; Analysis 7.7).

The NNTB was 2 (95% CI 1 to 5).

Subgroup analyses

Subgroup analysis of Analysis 7.7 according to type of gel and timing of second-look hysteroscopy revealed differences between comparison groups for use of HA gel at second-look hysteroscopy at nine to 12 weeks (OR 0.05, 95% CI 0.01 to 0.26, 55 participants, three studies, I^2 = 0%) but not poly gel at zero to four weeks (OR 0.09, 95% CI 0.00 to 3.59, seven participants, one study, I^2 = 0%) nor poly gel at five to eight weeks (OR 0.28, 95% CI 0.03 to 2.98, 41 participants, one study, I^2 = 0%) compared with no treatment for this outcome and showed no subgroup differences (Chi^2 = 1.34, df = 2 (P value = 0.51), I^2 = 0%; Analysis 7.7).

Data from this subgroup analysis should be treated with caution and should not be over-interpreted, as subgroup analysis by itself is observational in nature, and statistical interpretation of results is not without problems. Moreover, this subgroup analysis, although it made clinical sense, was a post hoc analysis.

Sensitivity analyses

A sensitivity analysis on the choice to include all studies regardless of study quality compared with the singleton study with low risk of bias (Roy 2014) revealed no substantial changes in the direction or magnitude of effect size nor in the statistical significance of differences between comparison groups for Analysis 7.1 and Analysis 7.3. For Analysis 7.4 and Analysis 7.2, a change in direction and/or a substantial decrease in effect size was demonstrated by sensitivity analyses comparing inclusion of all trials regardless of study quality versus the singleton study with low risk of bias; differences between comparison groups were not statistically significant. Therefore, the results of Analysis 7.4 and Analysis 7.2 are not robust.

We used surrogate outcomes (term delivery at 12 to 18 months for Abu Rafea 2013 and ongoing pregnancy for Roy 2014) for the primary outcome of live birth in Analysis 7.1. A sensitivity analysis on the choice to include only one study (Amer 2010) versus all three studies (Abu Rafea 2013; Amer 2010; Roy 2014) revealed no differences between treatment arms (OR 1.50, 95% CI 0.14 to 15.87, P value = 0.74, one study, 43 women).

In Abu Rafea 2013, some women (4/28, or 14% of participants) were not trying to conceive after treatment, although they had been randomly assigned (1/13 in the intervention group and 3/15 in the control group). We refer to data provided by a sensitivity analysis on the choice to use available data analyses rather than ITT analyses for Analysis 1.1. When an intention to treat analysis was performed, using the assumption that no live births occurred in women for whom outcome data were not available, our findings did not differ substantially from the results obtained when we analysed only the available data (ITT analysis: OR 1.08, 95% CI 0.51 to 2.27, P value = 0.85, three studies, 150 women; available data analysis: OR 0.99, 95% CI 0.46 to 2.13, P value = 0.98, three studies, 150 women). See Analysis 7.1

We excluded from further analyses data from 24 participants in the study by Di Spiezio Sardo 2011 who were undergoing endometrial ablation, as endometrial ablation/resection is not a fertility-enhancing intervention. We subjected this decision to a sensitivity analysis. We found no substantial impact on effect size or on tests of statistical significance when results from all participants were taken into account (OR 0.36, 95% CI 0.20 to 0.62, P value = 0.0003, five studies, 407 women) versus data from 24 women treated by endometrial ablation who were excluded for Analysis 7.4 (OR 0.37, 95% CI 0.20 to 0.67, P value = 0.0010, five studies, 383 women).

Multiple sensitivity analyses showed that results of the pooled analyses were independent of the choice of analysis model or summary effect measure.

8. Any therapy versus any other therapy

We included one study (Lin 2013).
See Characteristics of included studies.

Primary outcome

8.1 Live birth or ongoing pregnancy

We retrieved no randomised studies reporting this outcome.

Secondary outcomes

8.2 Clinical pregnancy

We retrieved no randomised studies reporting this outcome.

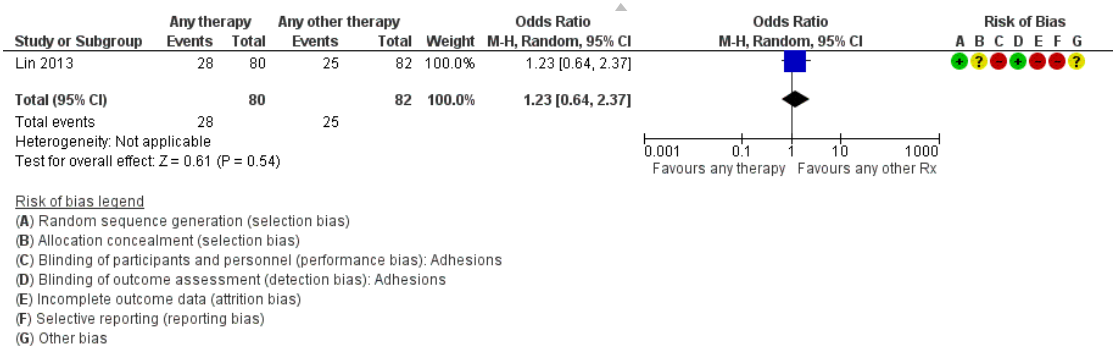
8.3 Miscarriage

We retrieved no randomised studies reporting this outcome.

8.4 Presence of intrauterine adhesions at second-look hysteroscopy

We found no evidence of differences between groups (OR 1.23, 95% CI 0.64 to 2.37, P value = 0.54, one study, 162 women; Analysis 8.1; Figure 6).

Figure 6. Forest plot of comparison: 8 Any therapy vs any other therapy, outcome: 8.1 Presence of intrauterine adhesions at second-look hysteroscopy.



No studies reported our other secondary outcomes.

Subgroup analyses

We conducted no subgroup analyses.

Sensitivity analyses

We conducted no sensitivity analyses.

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Any anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility vs any other anti-adhesion therapy

Patient or population: women treated by operative hysteroscopy for uterine pathology associated with subfertility
Settings: single centre - Hysteroscopy Unit of Department of Obstetrics and Gynaecology of a university or non-university tertiary care hospital
Intervention: insertion of an IUD followed by hormonal treatment
Comparison: insertion of a specially designed intrauterine balloon followed by hormonal treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Balloon	IUD				
Presence of intrauterine adhesions at second-look hysteroscopy (4 to 8 weeks)	Low-risk population[a]		OR 1.23 (0.64 to 2.37)	162 (1 study)	⊕◯◯◯ Very low[b,c,d]	
	0 per 1000	0 per 1000				
	Medium-risk population[a]					
	454 per 1000	521 per 1000 (334 to 811)				
	High-risk population[a]					
	875 per 1000	1004 per 1000 (645 to 1564)				

*The basis for the **assumed risk** is provided in the footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a] Assumed risk of low/medium/high-risk population based on presence of intrauterine adhesions following hysteroscopic removal of endometrial polyps/mean prevalence of intrauterine adhesions/removal of uterine septum, respectively, based on data from a prospective cohort study.
[b] Only 1 single-centre study retrieved.
[c] Several serious methodological limitations.
[d] Indirectness: limited proportion of women suffering from subfertility (26% in balloon group and 22% in IUD groups).

DISCUSSION

Summary of main results

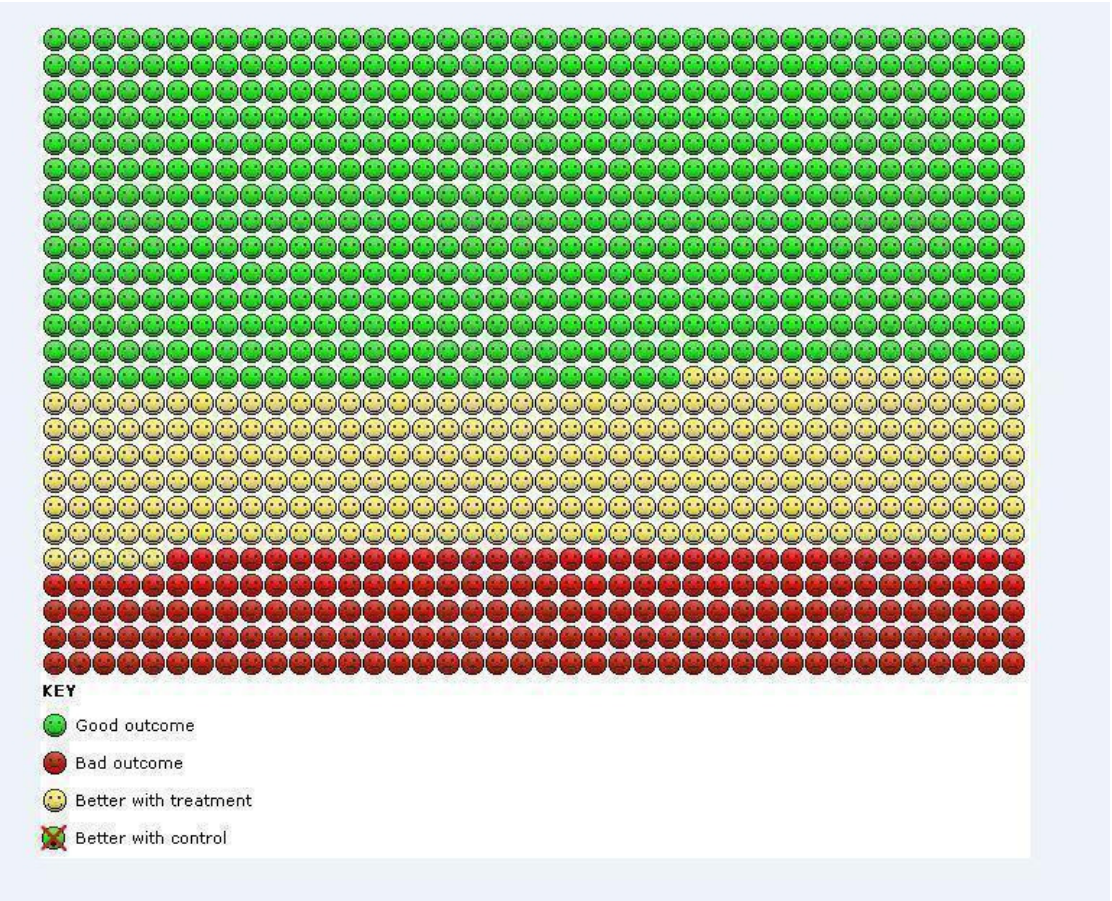
This systematic review aimed to investigate whether use of anti-adhesion therapy following operative hysteroscopy made a difference in the main outcomes of live birth or ongoing pregnancy, clinical pregnancy and miscarriage, or in the prevalence, extent or severity of intrauterine adhesions (IUAs) in women with subfertility. We searched for studies randomly comparing any anti-adhesion therapy versus no treatment or placebo following operative hysteroscopy. We also searched for studies randomly comparing any anti-adhesion therapy versus any other treatment.

We retrieved 11 randomised studies including 803 participants on use of an inserted device versus no treatment (two studies; 84 women) (Abu Rafea 2013; Lin 2015) or another inserted device (one study; 162 women) (Lin 2013), on use of hormonal treatment versus no treatment or placebo (two studies; 131 women) (Dabir-Ashrafi 1996; Roy 2014), on use of anti-adhesion barrier gels versus no treatment (five studies; 383 women) (Acunzo 2003; De Iaco 2003; Di Spiezio Sardo 2011; Fuchs 2014; Guida 2004) and on use of human amniotic membrane grafting versus no graft (one study; 43 women) (Amer 2010). The proportion of subfertile women varied from 0% (one study; 41 women), to less than 50% (six studies; 487 women), to 100% (one study; 43 women); the proportion was unknown in three studies (232 women). Most studies (9/11) had at least one item at high risk of bias.

Pooled analysis of findings from Abu Rafea 2013, Amer 2010 and Roy 2014 provided no evidence of differences between any anti-adhesion therapy following operative hysteroscopy versus no treatment or placebo for increasing live birth or ongoing pregnancy rates in women wishing to conceive. Findings of this meta-analysis are not influenced by study quality, as was demonstrated by a sensitivity analysis.

Pooled analysis of findings from Acunzo 2003, De Iaco 2003, Di Spiezio Sardo 2011, Fuchs 2014, Guida 2004, Lin 2015 and Roy 2014 revealed differences between arms that favoured use of any anti-adhesion therapy versus no treatment or placebo following operative hysteroscopy for the outcome of IUAs at any second-look hysteroscopy. For use of anti-adhesion barrier gels, we would expect that out of 1000 women treated by operative hysteroscopy, between 120 and 316 would develop IUAs, compared with 454 women when no gels were used (Figure 7). Pooled analysis of the findings of Acunzo 2003, De Iaco 2003, Di Spiezio Sardo 2011, Fuchs 2014 and Guida 2004 revealed that use of any anti-adhesion therapy versus no treatment or placebo is associated with an increase in the proportion of mild adhesions and a decrease in the proportion of moderate or severe adhesions at any second-look hysteroscopy.

Figure 7. Cates' plot of NNTB for Analysis 7.4, assuming medium risk of 454 women per 1000 with intrauterine adhesions at second-look hysteroscopy in the control group. Use of anti-adhesion barrier gels decreases the number of women with IUAs present at second look to 195 women per 1000. Figure drawn using http://www.nntonline.net.



Findings of Lin 2013 showed no effect and no benefit with either intervention - inserting an intrauterine device (IUD) or an intrauterine balloon - for the presence of IUAs at second-look hysteroscopy.

Overall completeness and applicability of evidence

We failed to retrieve studies that randomly compared insertion of an IUD versus no treatment; an IUD is very often inserted following hysteroscopic treatment of IUAs or the intrauterine septum in everyday clinical practice. We retrieved only one study that randomly compared any anti-adhesion therapy versus any other treatment following operative hysteroscopy.

Only three studies reported live birth or ongoing pregnancy rates (Abu Rafea 2013; Amer 2010; Roy 2014) - the primary outcomes of interest for women wishing to conceive. Four studies (Abu Rafea 2013; Amer 2010; Fuchs 2014; Roy 2014) reported data on the two other key reproductive outcomes - clinical pregnancy and miscarriage. Secondary outcomes of prevalence, mean adhesion scores and severity of IUAs at second-look hysteroscopy were reported in eight studies (Acunzo 2003; De Iaco 2003; Di Spiezio Sardo 2011; Fuchs 2014; Guida 2004; Lin 2013; Lin 2015; Roy 2014). Only eight studies reported data on the proportion of women suffering from subfertility (Abu Rafea 2013; Acunzo 2003; Amer 2010; Dabir-Ashrafi 1996; Di Spiezio Sardo 2011; Fuchs 2014; Lin 2013; Roy 2014). Out of 571 participants from these eight studies, only 188 women were suffering from subfertility (33%). Therefore, the evidence retrieved may be indirect for the target population prespecified for the present Cochrane review.

We did not retrieve cost-effectiveness studies on prevention of adhesion after operative hysteroscopy in a subfertile population.

In conclusion, we judged that the body of evidence retrieved is not sufficient to fully address all research questions predefined in this Cochrane review.

Quality of the evidence

Several limitations at study and outcome levels were related to performance bias, other potential sources of bias, attrition bias and reporting and selection bias in decreasing order of frequency. Reasons for risk of bias at the study level and across studies are discussed in detail in the section Risk of bias in included studies and are graphically presented in Figure 2 and Figure 3.

See Summary of findings for the main comparison.

We graded evidence as low quality for the randomised comparison of any anti-adhesion therapy versus no treatment or placebo for the outcome of live birth. Available evidence was derived from three single-centre studies including 150 women (Abu Rafea 2013; Amer 2010; Roy 2014). The design of Abu Rafea 2013 and Amer 2010 had several limitations. The third study (Roy 2014) was at low risk of bias. A sensitivity analysis on the choice to include all three studies regardless of study quality compared with the single study at low risk of bias revealed no substantial change in the direction or magnitude of effect size and in tests of statistical significance. Moreover, only some participants in the two included studies suffered from subfertility (5/28, or 18%, in Abu Rafea 2013, and 31/90, or 34%, in Roy 2014): Available evidence is therefore indirect. Results of Abu Rafea 2013 and Amer 2010 are imprecise, given the wide confidence intervals of the point estimate.

We graded evidence as very low for the randomised comparison of any anti-adhesion therapy versus no treatment or placebo for the outcome of IUAs present at second-look hysteroscopy. Included studies (Acunzo 2003; De Iaco 2003; Di Spiezio Sardo 2011; Fuchs 2014; Guida 2004; Lin 2015; Roy 2014) had several main limitations. Available evidence showed a substantial degree of indirectness: In two of the four Italian trials, 19% (Di Spiezio Sardo 2011) and 37% (Acunzo 2003) of participants suffered from subfertility; in two other Italian studies (De Iaco 2003; Guida 2004), it is unclear whether subfertile women were included even after primary study authors provided clarification; and in the fifth trial from Israel (Fuchs 2014), only women with proven fertility were included. We identified two single-centre studies (Lin 2015; Roy 2014) for the second subgroup of this randomised comparison. Lin 2015 was a small study with no events resulting in an undetermined treatment effect. It is not clear whether subfertile women were included in this study, and if so, how many. Only 34% of participants in Roy 2014 suffered from subfertility, which makes available evidence indirect. Results are very imprecise, given the very wide confidence intervals of the effect estimate. Formal study of reporting bias was not possible because of the small number of studies included for this randomised comparison.

See Summary of findings 2.

We graded evidence as very low quality for the randomised comparison of any anti-adhesion therapy versus any other anti-adhesion therapy for the outcome of IUAs present at second-look hysteroscopy. We included only one single-centre study (Lin 2013) with several serious methodological limitations: The study was at high risk of performance bias in relation to blinding of participants and personnel, was at high risk of attrition bias in relation to loss to follow-up of 17% of randomly assigned participants and was at high risk of bias for selective outcome reporting on the basis of discrepancies observed between the registered study protocol and findings of the published abstract of the study. Moreover, the study had several main methodological limitations. Moreover, the proportion of women truly suffering from subfertility was not reported.

Potential biases in the review process

Limitations at the review level include the following.

- We conducted no formal study of reporting bias because we retrieved a limited number of studies. Nevertheless, we aimed to minimise the potential impact of reporting and publication bias by conducting a comprehensive search for all potentially eligible studies, and by staying alert for duplication of data as predefined in the protocol of this Cochrane review (Bosteels 2013b). We consistently searched for related articles in published and secondary reports of included studies. We contacted all authors of included studies to ask if they were aware of any published or ongoing trials; we also contacted experts in the field.
- We rigorously subjected to sensitivity analyses all choices to include only studies at low risk of bias versus all studies, to use available data analyses rather than ITT analyses or to exclude participants who were treated by an intervention not indicated for treating subfertility; we considered any observed substantial changes when interpreting results.
- We used surrogate outcomes (term delivery at 12 to 18 months for Abu Rafea 2013 and ongoing pregnancy for Roy 2014) for the primary outcome of live birth; a sensitivity analysis on the choice to include only one study reporting live birth versus all three studies revealed no differences.
- At least two review authors extracted all data: JB extracted data from all studies, and TD/FB/JK/SW divided all studies between them, and each extracted data from only a portion of the studies. In cases of disagreement, BWM acted as a third review author for arbitration. This implies that JB may have had a big influence on the decisions, which might have introduced bias at the level of the review.

Agreements and disagreements with other studies or reviews

Three reviews support use of adhesion barriers for reducing the presence of IUAs at a second-look procedure. One Cochrane re-

view (Ahmad 2010) including 16 trials on gynaecological surgical interventions - six by laparoscopy and 10 by laparotomy - demonstrated benefit with use of an absorbable adhesion barrier in laparoscopic surgery for reducing the incidence of adhesions when compared with no treatment at second-look laparoscopy in both de novo adhesions (odds ratio (OR) 0.31, 95% confidence interval (CI) 0.12 to 0.79) and re-formed adhesions (OR 0.19, 95% CI 0.09 to 0.42). Similar benefit was demonstrated with use of an absorbable adhesion barrier for reducing the incidence of recurrent adhesions after adhesiolysis by laparotomy compared with no treatment (OR 0.39, 95% CI 0.28 to 0.55). Deans 2010 is a narrative review reporting findings and conclusions of a single RCT (Acunzo 2003) included in the present Cochrane review. Mais 2012 is a systematic review with a meta-analysis performed to study the effectiveness of auto-cross-linked polysaccharide (ACP) gel for adhesion prevention in laparoscopic and hysteroscopic surgery. Data from three RCTs (Acunzo 2003; De Iaco 2003; Guida 2004) included in our systematic search and critical appraisal of the literature were pooled: The proportion of women with adhesions at second look was significantly lower in women who received ACP gel than in the control group (RR 0.50, 95 % CI 0.31 to 0.85, P value = 0.009, three studies, 256 women). Mais 2012 used the Jadad scale - an older and less valid tool for assessing the validity of intervention studies - not the risk of bias tool: This explains the disagreement between the judgement of Mais 2012 that rated all included studies as 'high quality' and the present Cochrane review, which graded available evidence for the main outcomes as 'very low quality'. According to the authors of a small (N = 54 women) observational study (Ducarme 2006), use of ACP gel does not decrease the incidence or reduce the severity of IUAs following operative hysteroscopy. The target population was non-randomly divided into two comparison groups: Women in the intervention group A (N = 30) were treated by intrauterine application of ACP gel, whereas women in the control group received no further treatment (N = 24). Key outcomes included rate of adhesion formation, mean adhesion scores and severity of adhesion formation scored according to the 1988 AFS classification at second-look hysteroscopy two months following operative hysteroscopy. No statistically significant differences between comparison groups were noted in the rate of IUA formation (33.3%) nor in median adhesion scores (1.30 ± 2.35 in the intervention group vs 1.42 ± 2.47 in the control group; P value > 0.05) and severity of adhesions (70% stage I adhesions, 20% stage II adhesions and 10% stage III adhesions in the intervention group vs 62.5% stage I, 25% stage II and 12.5% stage III in the control group; P value > 0.05).

Three reviews support our conclusion that the body of evidence on the effectiveness of anti-adhesion treatment for improving key reproductive outcomes is at present not conclusive. Review authors of the Cochrane review (Ahmad 2010) report insufficient data to support use of absorbable adhesion barriers for improving pregnancy rates. According to the authors of a narrative review (Revaux 2008), widespread use of anti-adhesion barrier gels for preventing IUAs in subfertile women following operative hysteroscopy should not be recommended at the present; additional high-quality studies on the clinical effectiveness of barrier gels are needed because the body of evidence is not solid. A second narrative review (Warembourg 2015) advocates for improvement in surgical techniques, design of new intrauterine medical devices and additional basic research on endometrial stem cells as the way forward.

A recent systematic review (Salma 2014) including 28 observational studies of 1806 women with meta-analysis of five studies and qualitative assessment of 23 studies reported benefit with insertion of an IUD for all women with IUAs regardless of the severity of the IUAs. In the opinion of the authors of this review, use of IUDs should be combined with other anti-adhesion therapies 'to obtain maximal outcomes, in particular in patients with moderate to severe IUAs'. This review suffers from several methodological limitations, including lack of a formal assessment of risk of bias, lack of appreciation of the role of confounding variables, lack of adjustment for confounders in data calculation for pooled analyses, evidence of substantial statistical heterogeneity for pooled analyses of the five included studies and lack of formal assessment of reporting bias.

AUTHORS' CONCLUSIONS

Implications for practice

The quality of the evidence retrieved for all outcomes is low or very low. For daily clinical practice, the effectiveness of anti-adhesion treatment in improving key reproductive outcomes or in decreasing intrauterine adhesions following operative hysteroscopy in subfertile women remains uncertain.

Implications for research

Additional studies are needed to assess the effectiveness of different anti-adhesion therapies for improving reproductive outcomes in subfertile women treated by operative hysteroscopy.

Cost-effectiveness studies are needed to examine adhesion prevention after operative hysteroscopy in a subfertile population.

ACKNOWLEDGEMENTS

Cochrane Gynaecology and Fertility Group (CGF; formerly Cochrane Menstrual Disorders and Subfertility Group (MDSG)): We wish to thank Professor Cindy Farquhar, CGF Co-ordinating Editor and Ms Helen Nagels, CGF Managing Editor, for editorial review. Ms Marian Showell, CGF Trials Search Co-ordinator,

assisted in developing several of the search strategies used in the present review. We thank the referees for their remarks and criticisms during the peer review process; their efforts have increased the scientific value of the present Cochrane review.

Ms Elizabeth Bosselaers (Managing Secretary CEBAM, the Belgian Branch of the Dutch Cochrane Centre) for logistical support, language correction and assistance with the plain language summary. Ms Sofie De Wit (Managing Secretary Department of Obstetrics and Gynaecology, Imeldahospital Bonheiden, Belgium) for providing comments and criticisms on the content of the plain language summary section.

Dr. Pierandrea De Iaco (Italy), Dr. Murali Subbaiah (India), Prof. Dr. Attilio DiSpiezio Sardo (Italy), Dr. Mohamed Amer (Egypt) and Dr. Moty Pansky (Israel) for answering queries.

REFERENCES

References to studies included in this review

Abu Rafea 2013 *{published data only}*
Abu Rafea BF, Vilos GA, Oraif AM, Power SG, Hollet Cains J, Vilos AG. Fertility and pregnancy outcomes following resectoscopic septum division with and without intrauterine balloon stenting:a randomized pilot study. *Annals Saudi Medicine* 2013;**33**(1):34–9. [DOI: 10.5144/0256-4947.2013.34]

Acunzo 2003 *{published data only}*
Acunzo G, Guida M, Pellicano M, Tommaselli GA, Di Spiezio Sardo A, Bifulco G, et al. Effectiveness of auto-cross-linked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic adhesiolysis: a prospective, randomized, controlled study. *Human Reproduction* 2003;**18**(9):1918–21. [DOI: 10.1093/humrep/deg368; EMBASE: 2003371784 ; PUBMED: 12923149]

Amer 2010 *{published data only}*
Amer MI, Abd-El-Maeboud KHI, Abdelfatah I, Salama FA, Abdallah AS. Human amnion as a temporary biologic barrier after hysteroscopic lysis of severe intrauterine adhesions: pilot study. *Journal of Minimally Invasive Gynecology* 2010;**17**(5):605–11. [DOI: 10.1016/j.jmig.2010.03.019; PUBMED: 20576472]

Dabir-Ashrafi 1996 *{published data only}*
Dabir-Ashrafi H, Mohammad K, Moghadami-Tabrizi N, Zandinejad K, Moghadami-Tabrizi M. Is estrogen necessary after hysteroscopic incision of the uterine septum? . *The Journal of the American Association of Gynecologic Laparoscopists* 1996;**3**(4):623–5. [PUBMED: 9050699]

De Iaco 2003 *{published data only}*
De Iaco PA, Muzzupapa G, Bovicelli A, Marconi S, Bitti SR, Sansovini M, et al. Hyaluronan derivative gel (Hyalobarrier gel) in intrauterine adhesion (IUA) prevention after operative hysteroscopy. *Ellipse* 2003;**19**(1):15–8.

Di Spiezio Sardo 2011 *{published data only}*
Di Spiezio Sardo A, Spinelli M, Bramante S, Scognamiglio M, Greco E, Guida M, et al. Efficacy of a polyethylene oxide-sodium carboxymethylcellulose gel in prevention of intrauterine adhesions after hysteroscopic surgery. *Journal of Minimally Invasive Gynecology* 2011;**18**(4):462–9. [DOI: 10.1016/j.jmig.2011.04.007; PUBMED: 21777835]

Fuchs 2014 *{published data only}*
* Fuchs N, Smorgick N, Ben Ami I, Vaknin Z, Tovbin Y, Halperin R, et al. Intercoat (Oxiplex/AP gel) for preventing intrauterine adhesions after operative hysteroscopy for suspected retained products of conception: double-blind, prospective, randomized pilot study. *Journal of Minimally Invasive Gynecology* 2014;**21**(1):126–30. [PUBMED: 23954387]
Pansky M. Efficiency of Intercoat (Oxiplex/AP gel) in decreasing intrauterine adhesions [Intercoat (Oxiplex/AP gel) for preventing intrauterine adhesions following operative hysteroscopy for suspected retained products of conception – a prospective randomized pilot study]. World Health Organization International Clinical Trials Registry Platform search portal 2012. [CTG: NCT01377779]
Pansky M, Fuchs N, Ami I Ben, Tovbin Y, Halperin R, Vaknin Z, et al. Intercoat (Oxiplex/AP Gel) for preventing intrauterine adhesions following operative hysteroscopy for suspected retained products of conception - a pilot study. *Journal of Minimally Invasive Gynecology* 2011;**18**(S21):68.

Guida 2004 *{published data only}*
Guida M, Acunzo G, Di Spiezio Sardo A, Bifulco G, Piccoli R, Pellicano M, et al. Effectiveness of auto-crosslinked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic surgery: a prospective, randomized, controlled study. *Human Reproduction* 2004;**19**(6):1461–4. [DOI: 10.1093/humrep/deh238; PUBMED: 15105384]

Lin 2013 *{published and unpublished data}*

Lin X. A comparison of Cook balloon and coil in the prevention of adhesion reformation following hysteroscopic surgery for Asherman syndrome [A comparison of intrauterine balloon stent and intrauterine contraceptive device in the prevention of adhesion reformation following hysteroscopic surgery for Asherman syndrome: a randomized case–control study]. Controlled Trials. 2013. [ISRCTN: ISRCTN69690272]

Lin X, Wei ML, Li TC, Zhou F, Zhang SY. A prospective randomized control trial to compare the efficacy of intrauterine balloon and intrauterine contraceptive device in the prevention of adhesion reformation following hysteroscopic adhesiolysis. *Gynecological Surgery* 2014;**11** (Suppl 1:S1-S358):89-90 (ES23-O193). [DOI: 10.1007/s10397-014-0857-1]

* Lin XN, Zhou F, Wei ML, Yang Y, Li Y, Li TC, et al. Prospective, randomized, controlled trial comparing the efficacy of intrauterine balloon and intrauterine contraceptive device in the prevention of adhesion reformation after hysteroscopic adhesiolysis. *Fertility and Sterility* 2015;**104**(1):235–40. [DOI: 10.1016/j.fertnstert.2015.04.008]

Lin 2015 *{published data only}*

Lin YH, Jang TN, Hwang JL, Huang LW, Seow KM, Hsieh BC, et al. Bacterial colonization with balloon uterine stent placement in the uterus for 30 days: a randomized controlled clinical trial. *Fertility and Sterility* 2015;**103**(2): 513–8. [PUBMED: 25467040]

Roy 2014 *{published data only}*

Roy KK, Negi N, Subbaiah M, Kumar S, Sharma JB, Singh N. Effectiveness of estrogen in the prevention of intrauterine adhesions after hysteroscopic septal resection: a prospective, randomized study. *Journal of Obstetrics and Gynaecology Research* 2014;**40**(4):1085–8. [PUBMED: 13418076]

References to studies excluded from this review

Bednarek 2011 *{published data only}*

Bednarek PH, Creinin MD, Reeves MF, Cwiak C, Espey E, Jensen JT. Immediate versus delayed IUD insertion after uterine aspiration. *New England Journal of Medicine* 2011; **364**(23):2208–17. [DOI: 10.1056/NEJMoa1011600]

Hooker 2011 *{unpublished data only}*

Hooker AB. Post abortion prevention of adhesions: evaluation of hyaluronic acid, hyalobarier gel endo - PAPA- study [Het voorkomen van littekenvorming in de baarmoeder bij vrouwen die een curettage ondergaan vanwege een miskraam. (Evaluatie van anti–verklevingsmiddel).]. Netherlands Trial Register 2011. [: NTR3120]

Hu 2014a *{unpublished data only}*

Hu Y, Li X. Clinical study of the treatment of infertility caused by severe intrauterine adhesions by collagen scaffold loaded with autologous bone marrow stem cells [Clinical study of the treatment of infertility caused by severe intrauterine adhesions by collagen scaffold loaded with autologous bone marrow stem cells]. ChiCTR 2014. [: ChiCTR–OOC–14005571]

Hu 2014b *{unpublished data only}*

Hu Y, Li X. Clinical study of the treatment of infertility caused by severe intrauterine adhesions by collagen scaffold loaded with umbilical cord blood-derived mesenchymal stem cells [Clinical study of the treatment of infertility caused by severe intrauterine adhesions by collagen scaffold loaded with umbilical cord blood–derived mesenchymal stem cells]. ChiCTR 2014. [: ChiCTR–OPC–14005553]

Johns 2001 *{published data only}*

Johns DB, Keyport GM, Hoehler F, diZerega GS. Reduction of postsurgical adhesions with Intergel adhesion prevention solution: a multicenter study of safety and efficacy after conservative gynecologic surgery. *Fertility and Sterility* 2001;**76**(3):595–604. [DOI: S0015028201019549]

Kim 2012 *{published data only}*

Kim T, Ahn KH, Choi DS, Hwang KJ, Lee BI, Jung MH, et al. A randomized, multi-center, clinical trial to assess the efficacy and safety of alginate carboxymethylcellulose hyaluronic acid compared to carboxymethylcellulose hyaluronic acid to prevent postoperative intrauterine adhesion. *Journal of Minimally Invasive Gynecology* 2012;**19**(6):731–6. [DOI: 10.1016/j.jmig.2012.08.003; PUBMED: 23084677]

Kurtz 2002 *{published data only}*

Kurtz SM, Muratoglu OK, Gsell R, Greer K, Shen FW, Cooper C, et al. The role of Seprafilm™ bioresorbable membrane in the prevention and therapy of endometrial synechiae. *Journal of Biomedical Materials Research* 2002;**63** (1):10–4.

Letouzey 2014 *{unpublished data only}*

Letouzey V. Development of a bioabsorbable medical device for the prevention of postoperative intra-uterine adhesions. PréSynUT-1 [Pathophysiology of Intrauterine Synechia – Exploratory Study. Development of a Bioabsorbable Medical Device for the Prevention of Postoperative Intra–uterine Adhesions]. ClinicalTrials.gov 2014. [ISRCTN: NCT02328742]

Pabuccu 2008 *{published data only}*

Pabuccu R, Onalan G, Kaya C, Selam B, Ceyhan T, Ornek T, Kuzudisli E. Efficiency and pregnancy outcome of serial intrauterine device-guided hysteroscopic adhesiolysis of intrauterine synechiae. *Fertility and Sterility* 2008;**90**(5): 1973–7. [DOI: 10.1016/j.fertnstert.2007.06.074]

Tonguc 2010 *{published data only}*

Tonguc EA, Var T, Yilmaz N, Batioglu S. Intrauterine device or oestrogen treatment after hysteroscopic uterine septum resection. *International Journal of Gynecology and Obstetrics* 2010;**109**:226–9. [DOI: 10.1016/j.ijgo.2009.12.015]

Tsapanos 2002 *{published data only}*

Tsapanos VS, Stathopoulou LP, Papathanassopoulou VS, Tzingounis VA. The role of Seprafilm™ bioresorbable membrane in the prevention and therapy of endometrial synechiae. *Journal of Biomedical Materials Research* 2002;**63** (1):10–4. [PUBMED: 11787023]

Yaar 2004 *{published data only}*

Yaar L, Sönmez S, Koç S, Çebi Z, Küpelioğ lu L, Toklar A, ş ensoy Y. Prophylactic estrogen administration for preventing intrauterine adhesion formation following missed abortions. *Jinekoloji ve Obstetrik Dergisi 2004* 2004; **18**:154–7.

References to ongoing studies

Paz 2012 *{unpublished data only}*

Paz M, Lissak A. Efficiency of INTERCOAT (Oxiplex/AP Gel) in preventing intrauterine adhesion formation in hysteroscopic surgery [Efficiency of INTERCOAT (Oxiplex/AP Gel) in preventing intrauterine adhesion formation in hysteroscopic surgery – a prospective double blind randomized study]. ClinicalTrials.gov 2013. [NCT: 01637974; : CMC–11–0050–CTIL]

Revel 2011 *{unpublished data only}*

Revel A, Bechori H. Safety study of use of hyaluronic acid gel to prevent intrauterine adhesions in hysteroscopic surgery [Use of hyaluronic acid gel to prevent intrauterine adhesions in hysteroscopic surgery]. ClinicalTrials.gov 2011. [NCT: 01464528]

Additional references

Ahmad 2010

Ahmad G, Duffy JMN, Farquhar C, Vail A, Vanderkerchove P, Watson A, Wiseman D. Barrier agents for adhesion prevention after gynaecological surgery. *Cochrane Database of Systematic Reviews* 2008, Issue 2. [DOI: 10.1002/14651858.CD000475.pub2]

Amer 2006

Amer MI, Abd-El-Maeboud KH. Amnion graft following hysteroscopic lysis of intrauterine adhesions. *Journal of Obstetrics and Gynaecology Research* 2006;**32**(6):559–66. [DOI: 10.1111/j.1447-0756.2006.00454; PUBMED: 17100817]

Arora 1994

Arora M, Jaroudi KA, Hamilton CJ, Dayel F. Controlled comparison of Interceed and amniotic membrane graft in the prevention of postoperative adhesions in the rabbit uterine horn model. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 1994;**55**(3):179–82. [PUBMED: 7958162; SSDI: 0028–2243(94)01849–3]

Baakdah 2005

Baakdah H, Tulandi T. Adhesion in gynaecology complication, cost, and prevention: a review. *Surgical Technology International* 2005;**14**:185–90. [PUBMED: 16525972]

Badawy 1989

Badawy SZ, Baggish MS, ElBakry MM, Baltoyannis P. Evaluation of tissue healing and adhesion formation after an intra-abdominal amniotic membrane graft in the rat. *Journal of Reproductive Medicine* 1989;**34**(3):189–202. [PUBMED: 2724232]

Belluco 2001

Belluco C, Meggiolaro F, Pressato D, Pavesio A, Bigon E, et al. Prevention of postsurgical adhesions with an autocrosslinked hyaluronan derivative gel. *Journal of Surgical Research* 2001;**100**:217–21. [DOI: 10.1006/jsre.2001.6248; PUBMED: 11592796]

Binda 2007

Binda MM, Molinas CR, Bastidas A, Jansen M, Koninckx PR. Efficacy of barriers and hypoxia-inducible factor inhibitors to prevent CO(2)pneumoperitoneum-enhanced adhesions in a laparoscopic mouse model. *The Journal of Minimally Invasive Gynecology* 2007;**14**(5):591–9. [DOI: 10.1016/j.jmig.2007.04.002; PUBMED: 17848320]

Binda 2009

Binda MM, Koninckx PR. Prevention of adhesion formation in a laparoscopic mouse model should combine local treatment with peritoneal cavity conditioning. *Human Reproduction* 2009;**24**(6):1473–9. [DOI: 10.1093/humrep/dep053; PUBMED: 19258346]

Binda 2010

Binda MM, Koninckx PR. Hyperoxia and prevention of adhesion formation: a laparoscopic mouse model for open surgery. *British Journal of Obstetrics and Gynaecology* 2010;**117**(3):331–9. [DOI: 10.1111/j.1471-0528.2009.02370.x; PUBMED: 19832833]

Bosteels 2015

Bosteels J, Kasius J, Weyers S, Broekmans FJ, Mol BWJ, D'Hooghe TM. Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities. *Cochrane Database of Systematic Reviews* 2015, Issue 2. [DOI: 10.1002/14651858.CD009461.pub3]

Bristow 2007

Bristow RE, Santillan A, Diaz-Montes TP, Gardner GJ, Giuntoli RL, Peeler ST. Prevention of adhesion formation after radical hysterectomy using a sodiumhyaluronate-carboxymethylcellulose (HA-CMC) barrier: a cost-effectiveness analysis. *Gynecologic Oncology* 2007;**104**(3):739–46. [DOI: 10.1016/j.ygyno.2006.09.029; PUBMED: 7097723]

D'Hooghe 2009

D'Hooghe TM, Kyama CM, Chai D, Fassbender A, Vodolazkaia A, Bokor A, et al. Nonhuman primate models for translational research in endometriosis. *Reproduction Science* 2009;**16**(2):152–61. [PUBMED: 19208783]

De Iaco 1998

De Iaco PA, Stefanetti M, Pressato D, Piana S, Donà M, Pavesio A, et al. A novel hyaluronan-based gel in laparoscopic adhesion prevention: preclinical evaluation in an animal model. *Fertility and Sterility* 1998;**69**:318–23. [DOI: 10.1016/S0015-0282(98)00496-8; PUBMED: 9496348]

Deane 2013

Deane JA, Gualano RC, Gargett CE. Regenerating endometrium from stem/progenitor cells: is it abnormal in endometriosis, Asherman's syndrome and infertility?

. *Current Opinion in Obstetrics & Gynecology* 2013;**25**: 193–200. [DOI: 10.1097/GCO.Ob13e32836024e7]

Deans 2010

Deans R, Abbott J. Review of intrauterine adhesions. *The Journal of Minimally Invasive Gynecology* 2010;**17**: 555–69. [DOI: 10.1016/j.jmig.2010.04.016; PUBMED: 20656564]

DeCherney 1997

DeCherney AH, diZerega GS. Clinical problem of intraperitoneal postsurgical adhesion formation following general surgery and the use of adhesion prevention barriers. *Surgical Clinics of North America* 1997;**77**:671–88. [PUBMED: 9194886]

Diamond 1988

Diamond MP, DeCherney AH, Linsky CB, Cunningham T, Constantine B. Adhesion re-formation in the rabbit uterine horn model: I. Reduction with carboxymethylcellulose. *International Journal of Fertility* 1988;**33**:372–5. [PUBMED: 2904426]

diZerega 1994

diZerega GS. Contemporary adhesion prevention. *Fertility and Sterility* 1994;**61**:219–35. [PUBMED: 8299773]

Ducarme 2006

Ducarme G, Davitian C, Zarrouk S, Uzan M, Poncelet C. Interest of auto-crosslinked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic surgery: a case-control study. *Journal de Gynecologie, Obstetrique et Biologie de la Reproduction* 2006;**35**(7): 691–5. [DOI: JGYN-11-2006-35-7-0368-2315-101019-200606713; PUBMED: 17088770]

Farhi 1993

Farhi J, Bar-Hava I, Homburg R, Dicker D, Ben-Rafael Z. Induced regeneration of endometrium following curettage for abortion: a comparative study. *Human Reproduction* 1993;**8**:1143. [PUBMED: 8408501]

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**(7414):557–60. [DOI: 10.1136/bmj.327.7414.557; PUBMED: 12958120]

Hori 2006

Hori J, Wang M, Kamiya K, Takahashi H, Sakuragawa N. Immunological characteristics of amniotic epithelium. *Cornea* 2006;**25**(10 Suppl 1):S53–8. [PUBMED: 17001194]

Johary 2013

Johary J, Xue M, Zhu X, Xu D, Palani Velu P. The efficacy of estrogen therapy in patients with intrauterine adhesions: a systematic review. *The Journal of Minimally Invasive Gynecology* 2013;**Aug 8**:pii: S1553-4650(13)00426-3. [DOI: 10.1016/j.jmig.2013.07.018; PUBMED: 23933351]

Kelekci 2004

Kelekci S, Yilmaz B, Oguz S, Zergeroğ lu S, Inan I, Tokucoğ lu S. The efficacy of a hyaluronate/carboxymethylcellulose membrane in prevention of postoperative adhesion in a rat uterine horn model. *Tohoku Journal of Experimental Medicine* 2004;**204**:189–94. [DOI: 10.1620/tjem.204.189; PUBMED: 15502417]

Kodaman 2007

Kodaman PH, Arici A. Intra-uterine adhesions and fertility outcome: how to optimize success?. *Current Opinion in Obstetrics & Gynecology* 2007;**19**(3):207–14. [PUBMED: 17495635]

Koçak 1999

Koçak I, Unlü C, Akçan Y, Yakin K. Reduction of adhesion formation with cross-linked hyaluronic acid after peritoneal surgery in rats. *Fertility and Sterility* 1999;**72**:873–8. [DOI: 10.1016/S0015-0282(99)00368-4; PUBMED: 10560992]

Laurent 1992

Laurent TC, Fraser JRE. Hyaluronan. *The Journal of the Federation of American Societies for Experimental Biology* 1992;**6**:2397–404.

Leach 1998

Leach RE, Burns JW, Dawe EJ, SmithBarbour MD, Diamond MP. Reduction of postsurgical adhesion formation in the rabbit uterine horn model with use of hyaluronate/carboxymethylcellulose gel. *Fertility and Sterility* 1998; **69**(3):415–7. [DOI: 10.1016/S0015-0282(97)00573-6; PUBMED: 9531869]

Mais 2012

Mais V, Cirronis MG, Peiretti M, Ferrucci G, Cossu E, Melis GB. Efficacy of auto-cross linked hyaluronan gel for adhesion prevention in laparoscopy and hysteroscopy; a systematic review and meta-analysis of randomized controlled trials. *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 2012;**160**:1–5. [DOI: 10.1016/j.ejogrb.2011.08.002; PUBMED: 21945572]

Mascarenhas 2012

Mascarenhas MN, Flaxman SR, Boerma T, Vanderpoel S, Stevens GA. National, regional, and global trends in infertility prevalence since 1990: a systematic analysis of 277 health surveys. *PLoS Medicine* 2012;**9**(12):e1001356.

Meller 1999

Meller D, Tseng SC. Conjunctival epithelial cell differentiation on amniotic membrane. *Investigative Opthalmology and Visual Science* 1999;**40**:878–86. [PUBMED: 10102284]

Nappi 2007

Nappi C, Di Spiezio Sardo A, Greco E, Guida M, Bettocchi S, Bifulco G. Prevention of adhesions in gynaecological endoscopy. *Human Reproduction Update* 2007;**13**(4):1–16. [DOI: 10.1093/humupd/dml061; PUBMED: 17452399]

Nimrod 1992

Nimrod A, Ezra E, Ezov N, Nachum G, Parisada B. Absorption, distribution, metabolism and excretion of bacteria-derived hyaluronic acid in rats and rabbits. *Journal of Ocular Pharmacology* 1992;**8**:161–72. [PUBMED: 1506757]

Okulicz 2002
Okulicz WC. Regeneration. In: Glasser SR, Aplin JD, Giudice LC, Tabibzadeh S editor(s). *The Endometrium*. London: Taylor and Francis, 2002:110–20.

Orhue 2003
Orhue AAE, Aziken ME, Igbefoh JO. A comparison of two adjunctive treatments for intrauterine adhesions following lysis. *International Journal of Gynaecology and Obstetrics* 2003;**82**:49–56. [DOI: 10.1016/S0020-7292(03)00030-4; PUBMED: 12834941]

Padykula 1991
Padykula HA. Regeneration in the primate uterus: the role of stem cells. *Annals of the New York Academy of Sciences* 1991;**622**:47–56. [PUBMED: 2064204]

Rajab 2010
Rajab TK, Wallwiener M, Planck C, Brochhausen C, Kraemer B, Wallwiener CW. A direct comparison of Seprafilm, Adept, Intercoat, and Spraygel for adhesion prophylaxis. *Journal of Surgical Research* 2010;**161**:246–9. [DOI: 10.1016/j.jss.2008.11.839; PUBMED: 9375716]

Renier 2005
Renier D, Bellato PA, Bellini D, Pavesio A, Pressato D, Borrione A. Pharmacokinetic behaviour of ACP gel, an autocrosslinked hyaluronan derivative, after intraperitoneal administration. *Biomaterials* 2005;**26**:5368–74. [DOI: 10.1016/j.biomaterials.2005.01.053; MEDLINE: 5814135]

Revaux 2008
Revaux A, Ducarme G, Luton D. Prevention of intrauterine adhesions after hysteroscopic surgery. *Gynecologie, Obstetrique et Fertilité* 2008;**36**(3):311–7. [DOI: 10.1016/j.gyobfe.2007.11.014; PUBMED: 18308609; WoS: 000254969900012]

Salma 2014
Salma U, Xue M, Sayed AS, Xu D. Efficacy of intrauterine device in the treatment of intrauterine adhesions. *Biomedical Research International* 2014;**2014**:589296. [DOI: 10.1155/2014/589296]

Schenker 1982
Schenker JG, Margalioth EJ. Intrauterine adhesions: an updated appraisal. *Fertility and Sterility* 1982;**37**:593–610. [PUBMED: 6281085]

Schonman 2008
Schonman R, Corona R, Bastidas A, De Cicco C, Mailova K, Koninckx PR. Intercoat gel (Oxiplex): efficacy, safety, and tissue response in a laparoscopic mouse model. *The Journal of Minimally Invasive Gynecology* 2008;**16**(2):188–94. [DOI: 10.1016/j.jmig.2008.12.014; PUBMED: 19249707]

Shamiyeh 2007
Shamiyeh A, Danis J, Benkö L, Vattay P, Röth E, Tulipan L, et al. Effect of hyaluron derivate gel in prevention of postsurgical peritoneal adhesions - an experimental study in pigs. *Hepatogastroenterology* 2007;**54**(76):1121–4. [PUBMED: 17629052]

Szabo 2002
Szabo A, Haj M, Waxsman I, Eitan A. Evaluation of seprafilm and amniotic membrane as adhesion prophylaxis in mesh repair of abdominal wall hernia in rats. *European Surgical Research* 2002;**32**(2):125–8. [DOI: 10.1159/000008751; PUBMED: 10810219]

Taskin 2000
Taskin O, Sadik S, Onoglu A, Gokdeniz R, Erturan E, Burak F, et al. Role of endometrial suppression on the frequency of intrauterine adhesions after resectoscopic surgery. *The Journal of the American Association of Gynecologic Laparoscopists* 2000;**7**(3):351–4. [DOI: 10.1016/S1074-3804(05)60478-1; PUBMED: 10924629]

Trelford Sauder 1977
Trelford Sauder M, Trelford JD, Matolo NM. Replacement of the peritoneum with amnion following pelvic exenteration. *Surgery, Gynecology & Obstetrics* 1977;**145**:699–701. [PUBMED: 910213]

Wallwiener 2006
Wallwiener M, Brucker S, Hierlemann H, Brochhausen C, Solomayer E, Wallwiener C. Innovative barriers for peritoneal adhesion prevention: liquid or solid? A rat uterine horn model. *Fertility and Sterility* 2006;**86**(4 Suppl):1266–76. [DOI: 10.1016/j.jgyn.2014.10.014; PUBMED: 17008150]

Warembourg 2015
Warembourg S, Huberlant S, Garric X, Leprince S, De Tayrac R, Letouzey V. Prevention and treatment of intrauterine synechiae: review of the literature. *Journal de Gynecologie Obstetrique et Biologie de la Reproduction* 2015;**44**(4):366–79. [DOI: 10.1016/j.jgyn.2014.10.014; PUBMED: 25479692]

Wood 1964
Wood J, Pena G. Treatment of traumatic uterine synechias. *International Journal of Fertility* 1964;**9**:405–10. [PUBMED: 14145804]

Yang 2013
Yang JH, Chen MJ, Chen CD, Chen SU, Ho HN, Yang YS. Optimal waiting period for subsequent fertility treatment after various hysteroscopic surgeries. *Fertility and Sterility* 2013;**Feb 21**(pii):S0015-0282(13)00193-3 [Epub ahead of print]. [DOI: 10.1016/j.fertnstert.2013.01.137; PUBMED: 2343383]

Zegers-Hochschild 2009
Zegers-Hochschild F, Adamson GD, de Mouzon J, Mansour R, Nygren K, Sullivan E, et al. International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of ART terminology 2009. *Fertility and Sterility* 2009;**92**(5):1520–4. [DOI: 10.1016/j.fertnstert.2009.09.009; PUBMED: 19828144]

References to other published versions of this review

Bosteels 2013a
Bosteels J, Pelckmans S, Weyers S, Mol BWJ, D'Hooghe T. The effectiveness of anti-adhesion therapy following

operative hysteroscopy for treating female infertility: a systematic review and meta-analysis. *Human Reproduction (Oxford, England)* 2013;**28**(Suppl.1):i364.

Bosteels 2013b

Bosteels J, Weyers S, Kasius J, Broekmans FJ, Mol BWJ, D'Hooghe TM. Anti-adhesion therapy following operative hysteroscopy for treating female subfertility. *Cochrane Database of Systematic Reviews* 2014, Issue 5. [DOI: 10.1002/14651858.CD011110]

Bosteels 2014

Bosteels J, Weyers S, Mol BWJ, D'Hooghe T. Anti-adhesion barrier gels following operative hysteroscopy for treating female infertility: a systematic review and meta-analysis. *Gynecological Surgery* 2014;**11**(2):113–27. [DOI: 10.1007/s10397-014-0832-x; PUBMED: 24795547]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Abu Rafea 2013

Methods	Parallel-group randomised controlled trial Single centre, Obstetrics and Gynecology Department, King Saud University, Riyadh, Saudi Arabia Protocol was approved by the IRB Unclear whether statistical power calculation was done (query not answered) Unclear about funding and conflicts of interest (query not answered)
Participants	Number recruited: not stated. Number randomly assigned: 28 women Number excluded after randomisation: 4 women Number analysed: 24 women Women with infertility and/or adverse pregnancy outcomes diagnosed with intrauterine septum by HSG, sonohysterography and/or hysteroscopy were invited to participate in the study Inclusion and exclusion criteria were ill defined: Some women - 1 in the intervention group and 3 in the control group - were not trying to conceive after treatment, which indicates poor definition of inclusion and exclusion criteria Mean age and range (years): 29 years in the intervention group (23 to 38 years) and 32 years in the control group (22 to 40 years) Duration of the study is not reported (query not answered) Number of subfertile women was 3 in the intervention group and 2 in the control group; most women included in this study had a history of adverse pregnancy outcomes (miscarriage or preterm delivery)
Interventions	Randomised comparison between insertion of a no. 14 paediatric Foley catheter balloon for 5 days (N = 13) vs no catheter/balloon (N = 15) following hysteroscopic septum division Cervix was dilated to 10 mm, and all uterine septa were divided using a 26 French (9 mm diameter) resectoscope and a 30-degree lens (Karl Storz, Tüttlingen, Germany) with a monopolar electrode utilising 1.5% glycine as distension medium via an electronic fluid management system (Endomat, Karl Storz, Tüttlingen, Germany) and 120 watts of low-voltage (cutting current mode) waveform delivered by an ICC 350 Erbe electrosurgical unit (Erbe, Tüttlingen, Germany). No specific timing was used to perform the surgery with regards to the menstrual cycle. Resectoscopic metroplasty was carried out using a Collin (Karl Storz, Tuttlingen, Germany) monopolar knife electrode at 90 degrees. All women had general anaesthesia and concomitant laparoscopy and treatment of pelvic pathology including adhesiolysis and/or reduction/excision of endometriosis when indicated using a CO^2 laser and/or electrosurgery. None of the participants received preoperative endometrial thinning, antibiotic prophylaxis or adjuvant postoperative hormonal therapy No specific timing was used to perform the surgery with regards to the menstrual cycle Although it is reported that 2 women in the intervention group and 1 in the control group conceived after ART, whether other fertility treatments were offered and how these co-treatments were distributed among both comparison groups (query not answered)

Abu Rafea 2013 (*Continued*)

	remain unclear
Outcomes	Length of residual septum: This outcome was measured by HSG 12 weeks after operative hysteroscopy First-trimester loss, second-trimester loss, preterm delivery, term delivery, ectopic pregnancy: These outcomes were measured at 12 to 18 months after operative hysteroscopy
Notes	No distinction was made between primary and secondary outcomes. Whether reproductive outcomes were measured at 1 or more than 1 time points is unclear; variation in the time points at which reproductive outcomes were measured was 6 months Some women - 1 in the intervention group and 3 in the control group - were not trying to conceive after treatment; they should have been excluded from analysis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was based on a computer generated list of numbers (unconcealed)" Comment: probably done
Allocation concealment (selection bias)	High risk	Quote: "Randomization was based on a computer generated list of numbers (unconcealed)" Comment: no allocation concealment
Blinding of participants and personnel (performance bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome
Blinding of participants and personnel (performance bias) Adhesions	High risk	Quote: "After ethics approval and informed consent, 28 women were randomized in the operating room into having a no. 14 paediatric Foley catheter/balloon for five days (N = 13) versus no catheter/balloon (N = 15) following resectoscopic septum division. The Foley balloon was inflated with 5 mL of normal saline solution" Quote: "All patients were discharged the same day, and the patients with the Foley catheter/balloon were instructed to cut with scissors the end of the catheter at 5 days at home and remove the catheter themselves" Comment: Physicians and personnel were not blinded to the intervention

Blinding of outcome assessment (detection bias) Live birth, pregnancy or miscarriage	Low risk	Quote: "They were also instructed to avoid pregnancy until their first assessment in 3 months by HSG, and they were reassessed at 6 and 12 to 18 months for pregnancy outcomes" Comment: unequivocal outcome
Blinding of outcome assessment (detection bias) Adhesions	Unclear risk	Quote: "They were also instructed to avoid pregnancy until their first assessment in 3 months by HSG, and they were reassessed at 6 and 12 to 18 months for pregnancy outcomes" Quote: "We could not be certain that the < 1 cm septum, reported by the radiologist, in the balloon group was a recurrence or incomplete division at the time of metroplasty, but in the intention-to-treat (ITT) analysis, we considered this cavity as normal" Comment: no blinding of outcome assessors reported; unclear who did the assessment (query not answered)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "We could not be certain that the < 1 cm septum, reported by the radiologist, in the balloon group was a recurrence or incomplete division at the time of metroplasty but in the intention-to-treat (ITT) analysis, we considered this cavity as normal" Comment: no incomplete outcome data
Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective outcome reporting when abstract, methods and results were compared
Other bias	High risk	Quote: "Fertility and pregnancy outcomes at 12 to 18 months post metroplasty are shown in Table 4" Comment: Reproductive outcomes were measured over a considerable time period rather than at 1 predefined time point. It is unclear whether more measurements were taken at 18 months in 1 of the comparison groups Comment: Although it is reported that 2 women in the intervention group and 1 in the control group conceived after ART,

		whether other fertility treatments were provided and how these co-treatments were distributed among comparison groups were unclear Some women - 1 in the intervention group and 3 in the control group - were not trying to conceive after treatment; they should have been excluded from the final analysis because conducting an ITT on the basis of poor inclusion and exclusion criteria can increase risk of bias Comment: According to Table 1, mean age (range) in the intervention and control groups was 29 years (23 to 38 years) and 32 years (22 to 40 years) with P value = 0.59. Mean age difference should not be considered as clinically irrelevant. We judged that some evidence suggests baseline imbalance between comparison groups Comment: high risk of selection, performance and detection bias

Acunzo 2003

Methods	Parallel-group randomised controlled trial Single centre, Hysteroscopic Unit at the University of Naples "Frederico II" - Italy Protocol was approved by the IRB Unclear whether statistical power calculation was done (query not answered) Funding and conflicts of interest were not reported (query not answered)
Participants	Number recruited: 92 women Number randomly assigned: 92 women Number lost to follow-up: 8 women Number analysed: 84 women 92 women with irregular menses and intrauterine adhesions were referred to the Hysteroscopic Unit of the University of Naples "Federico II". All women with intrauterine adhesions at diagnostic hysteroscopy were invited to participate in the study Inclusion criterion was hysteroscopic diagnosis of intrauterine adhesions Exclusion criteria included age > 50 years, weight > 100 kg, menopause (FSH > 40 mIU/mL, 17β-oestradiol < 20 pg/mL) or pregnancy (positive β-hCG test), presence of uterovaginal prolapse and severe urinary symptoms, presence of malignancy, presence of severe intercurrent illness (coagulation disorders, systemic disease, severe cardiopathy), presence of other intrauterine lesions (i.e. polyps, myomata, septa) Study duration: 15 months (from June 2001 to September 2002) Mean age (± SD) of study participants was 30.1 years (± 3.5 years) Number of subfertile women was 18 in the intervention group and 16 in the control group

Interventions	Randomised comparison between application of ACP gel (group A or intervention group: N = 46) and no application of ACP gel (group B or control group: N = 46) following hysteroscopic adhesiolysis Treatment group received intrauterine application of 10 mL of ACP gel (Hyalobarrier Gel; Baxter, Pisa, Italy) under hysteroscopic view after operative hysteroscopy The only intervention provided to the control group was hysteroscopic resection of intrauterine adhesions Diagnostic hysteroscopy was performed with a 3.5-mm instrument (Gynecare Versascope; Gynecare, Ethicon Inc., Somerville, NJ, USA) with normal saline solution (NaCl 0.9 %) used as the distension medium Operative hysteroscopy was performed with a rigid resectoscope (Karl Storz, Tuttlingen, Germany) with a 12-degree fore-oblique telescope and a hook-shaped monopolar electrode Women in both groups were administered oral antibiotics (cefixime 400 mg/d) (Cefixoral; Menarini, Firenze, Italy) for 3 days after surgery
Outcomes	Incidence of de novo adhesions, mean adhesion score and severity of adhesions according to the 1988 AFS classification system; all outcomes were measured after 3 months
Notes	Individual data on subfertile participants were not presented separately (query not answered)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Following diagnostic hysteroscopy, patients were randomized into two groups: group A (N = 46), the treatment group, and group B (N = 46), the control group, using a computer-generated randomisation list" Comment: probably done, as the same team of investigators has published data from a similar randomised trial
Allocation concealment (selection bias)	Unclear risk	Comment: method not described (query not answered)
Blinding of participants and personnel (performance bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome
Blinding of participants and personnel (performance bias) Adhesions	High risk	Quote: "Ultrasound scans were performed in each patient from group A immediately after ACP gel application and after 24, 48 and 72 hours. The gel-related hyperechoic thickness that seemed to separate endome-

		trial walls was the mean evaluated parameter" Comment: no blinding of participants and personnel to the intervention
Blinding of outcome assessment (detection bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome
Blinding of outcome assessment (detection bias) Adhesions	Unclear risk	Quote: "Both the initial diagnostic hysteroscopy and the 3-month follow-up diagnostic hysteroscopy were performed by the same operator (G.A.). G.A. evaluated the adhesion score for each patient and was blind for patients' randomized allocation, whilst operative hysteroscopies and application of ACP gel were performed by a different operator (M.G.)" Comment: method not described (query not answered)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Eight women (three from group A and five from group B) did not attend for follow-up hysteroscopy" Comment: unlikely to cause substantial attrition bias
Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective outcome reporting when abstract, methods and results were compared
Other bias	Low risk	Comment: no evidence of imbalance in baseline participant characteristics - no co-treatment

Amer 2010

Methods	Parallel-group randomised controlled trial with 3 comparison groups Single centre - Department of Obstetrics and Gynecology of the Ain Shams Medical School, Cairo, Egypt Protocol was approved by the IRB No statistical power calculation (query clarified by Dr. Mohamed Amer) No external funding and no conflicts of interest (query clarified by Dr. Mohamed Amer)
Participants	Number recruited: 45 women Number randomly assigned: 45 women Number lost to follow-up: 2 women Number analysed: 43 women Study was conducted from June 2004 to August 2009 in 45 women with severe IUAs

	diagnosed at office hysteroscopy. Infertility was the primary symptom, followed by hypomenorrhoea or amenorrhoea. Comprehensive infertility workup was performed, and women with other causes of subfertility and those with adhesions limited to the lower uterine segment or the upper cervical canal were excluded Study duration: 62 months (from June 2004 to August 2009) Median participant age (range) was 30.4 years (26 to 40 years)
Interventions	Participants were randomly assigned preoperatively by a computer-generated randomisation sheet to 3 groups of 15 women each. Allocation to any group was concealed in an opaque envelope, which was opened at the time of operation. Group 1 received an intrauterine balloon without amniotic graft, group 2 received fresh amnion and group 3 received dried amnion Two misoprostol tablets - 200 mg - were inserted vaginally the night before the operation to facilitate cervical dilation Operative hysteroscopy was performed with the participant under general anaesthesia in the follicular phase of the menstrual cycle; however, for women with amenorrhoea, no special time was chosen. Simultaneous laparoscopy was performed in women with infertility if they had not undergone a laparoscopy before, in those with previous complications of hysteroscopy such as uterine perforation and in those in whom uterine perforation occurred during the present procedure. Hysterometry with uterine sounding was followed by lysis of IUAs using 5F pointed tip semirigid scissors in a 5-mm rigid office hysteroscope, based on a 2.9-mm telescope (Karl Storz GmbH & Co. KB). In women with thick fibrous adhesions, adhesiolysis was performed using a 9-mm working element along with a sheath and a 4-mm 30-degree telescope (Karl Storz GmbH & Co. KB) equipped with a hysteroscopic monopolar knife (Collin operating knife) after cervical dilation to Hegar 9. Visualised adhesions were incised with 50- to 100-W cutting current, adjusted according to visual tissue effects, from an isolated electrosurgical generator (Valleylab SSE2L; Valleylab, Inc., Boulder, CO). Glycine 1.5% (Glycocolle 1.5%; Aguettant Laboratory, Lyon, France) was used as distension medium, with intrauterine pressure between 120 and 150 mm Hg, automatically controlled using a Hamou Hysteromat (Karl Storz GmbH & Co KB) with termination of the procedure if fluid deficit exceeded 1 L Freeze-dried amniotic membrane was hydrated using normal saline solution in a pan for 10 minutes before use Previously prepared fresh amniotic graft was washed several times with sterile normal saline solution before application. Amniotic graft was cut to form a 5 × 5-cm piece. This was spread on the balloon end of an 8F paediatric Foley catheter, so that the epithelial or basement membrane surface would be on top facing outward, where the inflated balloon acts as a mold for the amnion. The catheter tip with the amnion on its surface was then introduced into the inside of the uterine cavity with the aid of a straight artery forceps. The balloon was inflated with 3 to 5 mL of saline solution. A loose knot was made in the catheter stem, which was then slipped upward to just below the inflated balloon, then was tightened with the aid of the artery forceps, and the catheter stem was cut with scissors just below the knot after the catheter stem was stretched so that the balloon with the graft on its surface was kept intrauterine. In women with a patulous cervix that would not keep the inflated balloon inside the uterus, a cervical cerclage using braided polyester tape (Matrix Health Care SAE, Ameco, Egypt) was applied; it was removed later with the balloon. Postoperatively, ethinyl oestradiol tablets (Laboratoires Cassenne,

	Puteaux, France), 50 μg/d, were administered for 50 days Two weeks postoperatively, the balloon was removed transcervically with a crocodile forceps and with the participant under paracervical anaesthesia (lidocaine 2%, 6 mL, plus atropine, 0.5 mg, in the same syringe), as an outpatient procedure without cervical dilation. In women who had cervical cerclage, the tape was removed at the time of balloon extraction Second-look hysteroscopy was performed 2 to 4 months postoperatively by an independent observer blinded to the method. Outcome measures assessed included improvement in adhesion grade, improvement in menstruation, increased uterine length at sounding and complications. Subsequently, follow-up was provided via direct contact or by telephone every 3 months for a mean (range) of 28 months (6 to 60 months) for menstrual pattern and fertility
Outcomes	Ongoing pregnancy rate, clinical pregnancy rate, adhesion score, menstruation in days, improvement of menstruation in days, uterine length in centimetres, uterine length increase in centimetres, adhesion score improvement; some outcomes (improvement in adhesion grade, improvement in menstruation, increased uterine length at sounding and complications) were assessed between 2 and 4 months after surgery, whereas other outcomes were assessed via direct contact or by telephone every 3 months for a mean (range) of 28 months (6 to 60 months) for menstrual pattern and fertility
Notes	* Correspondence with authors on 04-01-2015: *Dear Dr. Jan Bosteels,* *Thanks for your e-mail and being interested in intrauterine adhesions management.* *1. The first study is a pilot study and not a randomized study (Amer MI, Abd-El-Maeboud KH. Amnion graft following hysteroscopic lysis of intrauterine adhesions J Obstet Gynaecol Res 2006; 32(6): 559-66).* *2. I confirm that these two studies are different and no patients in the second study were involved in the first study.* *3. It was a single-blinded; only the first surgeon knew if the graft was used or not and which type; also the patient, but the assessor, did not know which group of patients he is assessing.* *4. Analyses were conducted using commercially available software (SPSS for Windows, release 15.0; SPSS, Inc., Chicago, IL). All P values refer to 2-tailed tests of significance, with P 0. 05 considered significant. Data are given as count and percentage for categorical variables. Groups were compared using the c2 test and Fisher's exact test for categorized variables. For comparison of menstruation, uterine length and adhesion score, the Kruskal-Wallis test was used. Data are given as median (interquartile range [IQR]; 25th to 75th percentile). Pairwise comparison was performed using the Mann-Whitney test with Bonferroni correction. The critical level of significance was 0.02).* *5. There was no funding for the present study.* *6. There was no conflict of interest.* *7. To my knowledge, I do not know that there are new anti-adhesion therapy following operative hysteroscopy.* *With my best wishes.* *Dr. Mohamed I Amer*

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized preoperatively using a computer-generated randomisation sheet into 3 groups of 15 women each" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "Allocation to any group was concealed in an opaque envelope, which was opened at the time of operation" Comment: probably done
Blinding of participants and personnel (performance bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome
Blinding of participants and personnel (performance bias) Adhesions	High risk	Quote: "It was a single blinded, only the first surgeon that know if the graft used or not and which type also the patient, but the assessor did not know which group of patients he is assessing" (query clarified by Dr. Mohamed Amer) Comment: Method of blinding of participants and personnel is not described
Blinding of outcome assessment (detection bias) Live birth, pregnancy or miscarriage	Low risk	Quote: "This was a pilot, randomized, comparative study with blinded independent evaluation of changes in adhesion grade, menstruation, uterine length, number of operations needed to achieve a functional uterine cavity, reproductive outcome, and complications" Quote: "A second-look hysteroscopy was performed 2 to 4 months postoperative by an independent observer blinded to the method" Comment: unequivocal outcome
Blinding of outcome assessment (detection bias) Adhesions	Low risk	Quote: "This was a pilot, randomized, comparative study with blinded independent evaluation of changes in adhesion grade, menstruation, uterine length, number of operations needed to achieve a functional uterine cavity, reproductive outcome, and complications" Quote: "A second-look hysteroscopy was performed 2 to 4 months postoperative by an independent observer blinded to the method"

		Quote: "It was single blinded - only the first surgeon knew if the graft was used or not and which type, also the patient, but the assessor did not know which group of patients he was assessing" (query clarified by Dr. Mohamed Amer) Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Of the 45 patients included in the study, 2 were lost to follow-up (1 each in groups 1 and 2) and were excluded from analysis" Comment: unlikely to cause attrition bias
Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective outcome reporting when abstract, methods and results were compared
Other bias	High risk	Baseline imbalance in participant characteristics concerning cesarean section likely, as cause of intrauterine adhesions Quote: "Simultaneous laparoscopy was performed in women with infertility if they did not undergo laparoscopy before, in those with previous complications of hysteroscopy such as uterine perforation or if uterine perforation occurred during the present procedure" Comment: Co-treatment by laparoscopy and distribution in numbers among comparison groups is not stated Quote: "All pregnancies were spontaneous except 3 that were achieved after in vitro fertilization (IVF). One pregnancy was terminated at 7 weeks' gestation because of a blighted ovum. Two patients underwent IVF treatment twice, but did not conceive. The other patients could not afford the cost of IVF" Comment: co-treatment with IVF in some women, resulting in 3 pregnancies; no available data on distribution of co-treatment among the 3 comparison groups. Potential for performance bias

Dabir-Ashrafi 1996

Methods	Parallel-group randomised controlled trial Single centre - a national referral university hospital in Tehran, Iran Protocol approval by the IRB was not reported (query not answered) Unclear whether statistical power calculation was done (query not answered) Funding and conflicts of interest were not reported (query not answered)
Participants	Number recruited: 59 women Number excluded before randomisation: 13 women (9 women had abnormal findings at workup; 4 women were excluded because the angle between cervix and corpus could not be corrected) Number randomly assigned: 46 women Number lost to follow-up: 0 women Number analysed: 46 women 59 women with subfertility (15 women) and habitual abortion (44 women) were found to have a fundal defect on hysterosalpingography. They underwent a workup that included sperm analysis, assessment for infectious diseases (toxoplasmosis, *Listeria monocytogenes*, *Mycoplasma hominis*, syphilis), karyotyping, hormone profile (thyroxine, triiodothyronine, thyroid-stimulating hormone, T3 resin uptake, prolactin) and mid luteal progesterone assay. The 50 women whose examinations were normal and in whom the diagnosis of septate uterus was confirmed by laparoscopy participated in this study Study duration: onset and end dates of the study not reported Age in comparison groups was 26.7 years ± 6.5 years versus 28.4 years ± 4.5 years; it was not reported whether these numbers are means or medians with standard deviations
Interventions	All women underwent hysteroscopic incision of the septum with mini scissors. All septal incisions were performed by 1 surgeon, who was unaware of the group to which a participant had been assigned. Ampicillin 1 G was injected 1 hour before all operations, which were performed under general endotracheal anaesthesia. Distending medium was 5% dextrose in water. Blood pressure cuff was wrapped around the plastic bottle to raise the pressure of the medium. Procedures were performed with a 7-mm hysteroscope under laparoscopic guidance Randomised comparison between oestrogen treatment (N = 23) vs no hormonal treatment (N = 23) after operative hysteroscopy. Group 1 received conjugated oestrogen 1. 25 mg/d 30 days beginning on the day of the operation. For the last 7 days, they also took medroxyprogesterone acetate two 5-mg tablets/d. Group 2 received no hormone. A splint was not used in either group
Outcomes	Difference between ratios of length of septum to length of uterus in HSGs obtained preoperatively and postoperatively; this outcome was directly measured on HSG on cessation of menstruation 1 month after the procedure
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomized into two groups of 23 women each"

Dabir-Ashrafi 1996 (*Continued*)

		Comment: method not stated (query not answered)
Allocation concealment (selection bias)	Unclear risk	Quote: "All septal incisions were performed by one surgeon, who was unaware of the group to which a patient had been assigned" Comment: method not stated (query not answered)
Blinding of participants and personnel (performance bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome; no live birth or pregnancy rates reported
Blinding of participants and personnel (performance bias) Adhesions	Unclear risk	Quote: "The patients were randomized into two groups of 23 women each. Group 1 received conjugated oestrogen 1.25 mg/d 30 days beginning on the day of the operation. For the last 7 days, they also took medroxyprogesterone acetate two 5-mg tablets/d. Group 2 received no hormone" Comment: unclear whether placebo pills were used to blind participants and personnel (query not answered)
Blinding of outcome assessment (detection bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome; no live birth or pregnancy rates reported
Blinding of outcome assessment (detection bias) Adhesions	Unclear risk	Quote: "Directly on cessation of menstruation 1 month after the procedure, HSG was done and the results were compared with those of the preoperative HSG" Comment: outcome assessors not identified in the report - method of blinding not reported (query not answered)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Four were omitted from the analysis because the angle between the cervix and the uterine corpus could not be corrected, as shown by HSG" Comment: 4/50 (8%) participants were excluded; distribution among comparison groups was not reported (query not answered)

Dabir-Ashrafi 1996 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective outcome reporting when abstract, methods and results were compared
Other bias	Low risk	No evidence of baseline imbalance in participant characteristics

De Iaco 2003

Methods	Parallel-group randomised controlled trial Single centre - Department of Obstetrics and Gynecology of the University of Bologna - Italy Protocol was approved by the IRB No statistical power calculation for all outcomes (query clarified by Dr. Pierandrea De Iaco) No external funding and no conflicts of interest (query clarified by Dr. Pierandrea De Iaco)
Participants	Number recruited: 60 women Number randomly assigned: 60 women Number lost to follow-up: 20 women Number analysed: 40 women Quote: "Women were eligible for inclusion if they were undergoing endometrial ablation or hysteroscopic removal of submucosal fibroids, endometrial polyps, septate uterus or intrauterine synechiae" Comment: source population not adequately described in numbers and characteristics Quote: "Despite this, newly induced synechiae were less severe in the Hyalobarrier gel treated patients, thus reducing the risk of pregnancy morbidity and improving the outcomes of hysteroscopic surgery" Comment: not mentioned whether women suffered from infertility, and if so, how many; some subfertile women might have been included Study duration: 36 months: 1998 to 2001 (query clarified by Dr. Pierandrea De Iaco) Age of participants: ranged from 18 to 65 years
Interventions	Application of Hyalobarrier gel in the intervention group (N = 18 women analysed) versus no adhesion prevention treatment in the control group (N = 22 women analysed) . Number of women randomly assigned to each group not reported and not clarified by study authors Gel was applied with a 20-cm-long cannula with a diameter of 5 mm to cover the entire uterine cavity. Average volume of 10.5 ± 5.5 mL Hyalobarrier gel (range 5 to 20) was applied in the uterine cavity No adhesion prevention measures were used in the control group An 8-mm hysteroscopic resectoscope (Storz, Tuttlingen, Germany) with electrosurgical tips was used. In all cases, sorbitol-mannitol (Clear-Flex, Baxter S.A., Lessines, Belgium) was used as distension medium; fluid intake and output were continuously monitored (Hysteromat, Storz) Second-look hysteroscopy was undertaken 9 weeks after the initial procedure by a blinded investigator after insertion into uterine cavity with a 5-mm hysteroscope (Storz) with

	CO^2 distension
Outcomes	Incidence of de novo adhesions and severity of adhesions according to ASRM modified scoring system: all outcomes measured after 9 weeks
Notes	* The ASRM modified scoring system distinguishes only between stage I (mild) and stage II (severe) adhesions - different from the AFS 1988 classification system for intrauterine adhesions * Correspondence with authors on 09-12-2014: *Dear Dr. Jan Bosteels* *I have to admit that I have some difficulties in finding the data you are asking about research details. Anyway, these are my answers:* *1. no statistical power had been used before the trial.* *2. no funding, nor conflict of interest were present.* *3. I have some difficulties in telling the precise period. I say: 1998-2001.* *4. patients were randomly allocated using a random table (from literature).* *5. Dr. De Iaco performed the hysteroscopic surgery, while Dr. Muzzupapa performed the second-look hysteroscopy without knowing the group of treatment.* *6. I am not aware of ongoing studies about the same issue.* *Sincerely yours* *Pierandrea* *Dr. Pierandrea De Iaco* *Responsabile SSD Oncologia Ginecologica* *Policlinico Sant'Orsola-Malpighi* *Via Massarenti 13 - 40138 Bologna* *Fax 0516364392* *Cell. 3356666354*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After completion of the surgical procedure, the patients who met the inclusion criteria were randomly assigned either to the treatment with Hyalobarrier gel or to the control group, according to a computer-generated randomisation schedule" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Quote: "patients were randomly allocated using a random table" (query clarified by Dr. Pierandrea De Iaco) Comment: method of allocation concealment not described

Blinding of participants and personnel (performance bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome
Blinding of participants and personnel (performance bias) Adhesions	Unclear risk	Quote: "Dr. De Iaco performed the hysteroscopic surgery, while dr. Muzzupapa performed the second-look hysteroscopy without knowing the group of treatment" (query clarified by Dr. Pierandrea De Iaco) Comment: method of blinding of participants and personnel not described
Blinding of outcome assessment (detection bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome
Blinding of outcome assessment (detection bias) Adhesions	Low risk	Quote: "Second look hysteroscopy was undertaken nine weeks after the initial procedure by a blinded investigator after insertion in the uterine cavity of a 5 mm hysteroscope (Storz) with CO^2 distension" Quote: "Dr. De Iaco performed the hysteroscopic surgery, while Dr. Muzzupapa performed the second-look hysteroscopy without knowing the group of treatment" (query clarified by Dr. Pierandrea De Iaco) Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Sixty patients aged from 18 to 65 years old were enrolled in the study and written, informed consent was obtained from each patient" Quote: "A total of 40 patients attended the postoperative diagnostic hysteroscopy, 18 in the intervention and 22 in the control group" Comment: loss to follow-up of 20 out of 60 enrolled participants - very likely to cause substantial attrition bias
Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective outcome reporting when abstract, methods and results were compared
Other bias	High risk	Quote: "In conclusion, the authors recognize that the data reported lack statistical significance given the small sample size of the population evaluated. Despite this,

De Iaco 2003 (*Continued*)

		newly induced synechiae were less severe in the Hyalobarrier gel treated patients, thus reducing the risk of pregnancy morbidity and improving the outcomes of hysteroscopic surgery" Comment: Our own recalculation demonstrates that differences are not statistically significant; primary study authors' conclusions are not based on results Baseline characteristics in both comparison groups not explicitly presented; P values not given

Di Spiezio Sardo 2011

Methods	Parallel-group randomised controlled trial Single centre - Hysteroscopic Unit of the University of Naples "Frederico II" - Italy Protocol was approved by the IRB Statistical power calculation for primary outcome of incidence of de novo adhesions (query clarified by Dr. Attilio DiSpiezio Sardo) No external funding and no conflicts of interest (query clarified by Dr. Attilio DiSpiezio Sardo)
Participants	Number recruited: 136 women Number excluded before randomisation: 26 women (8 women declined after explanation of study protocol; 18 women were excluded because they were not willing to undergo surgery) Number randomly assigned: 110 women Number lost to follow-up: 0 women Number excluded after randomisation: 24 women. In the intervention group 11/55 women and in the control group 13/55 women were treated with endometrial ablation for resistant dysfunctional bleeding; these 24 participants were excluded from analyses, as endometrial ablation/resection is not indicated as a fertility-enhancing surgical intervention. This judgement was subjected to several sensitivity analyses Number analysed: 86 women All premenopausal women diagnosed at office diagnostic hysteroscopy (N = 136) with single or multiple lesions suitable for surgical treatment or with resistant dysfunctional uterine bleeding requiring endometrial ablation were invited to participate in the study. Of 26 women who declined to participate, 8 declined after explanation of study protocol, and 18 were excluded because they were not willing to undergo surgery. Between September 2008 and June 2009, 110 premenopausal women were enrolled in the study Exclusion criteria included body mass index > 30, menopause (follicle-stimulating hormone concentration > 40 mIU/mL and 17β-oestradiol < 20 pg/mL) or pregnancy (positive β-human chorionic gonadotropin test results), uterovaginal prolapse and severe urinary symptoms, malignancy or other serious concurrent condition (e.g. coagulation disorders, systemic disease, severe cardiac disease). Preexisting IUAs were considered an exclusion criterion because evaluation of re-formed IUAs was not the focus of the study Number of subfertile women with or without abnormal uterine bleeding was 12 in the

	intervention group and 9 in the control group; not possible to obtain individual outcome data for this small subgroup of subfertile women for IPD analysis (query clarified by Dr. Attilio DiSpiezio Sardo) Duration of study: 10 months: between September 2008 and June 2009 Mean age (± SD) in intervention group: 37 years (± 3.1 years) Mean age (± SD) in control group: 36 years (± 2.9 years)
Interventions	After surgery, group 1 or the intervention group (N = 55) underwent intrauterine application of 10 mL Intercoat gel under hysteroscopic guidance through inflow channel of resectoscope while operator gradually moved resectoscope from fundus of the uterus back to external uterine ostium to apply gel throughout the cavity and the cervical canal. Procedure was considered complete when, under hysteroscopic visualisation, the gel seemed to have replaced all of the liquid medium, and the cavity appeared completely filled by gel from the tubal ostia to the external uterine orifice In group 2 or control group (N = 55), only hysteroscopic surgery was performed Office diagnostic hysteroscopy was performed with a 5-mm-diameter continuous-flow hysteroscope with oval profile, a 30-degree fore-oblique telescope and a 5F operating channel (Karl Storz GmbH & Co. KG, Tuttlingen, Germany). Saline solution was used as distension medium (0.9% NaCl) and was administered through an electronic system of irrigation/aspiration (Endomat; Karl Storz GmbH & Co. KG) Operative hysteroscopy was performed with a rigid 27F resectoscope with a 30-degree fore-oblique telescope with various bipolar loops and a bipolar energy source (Versapoint; Gynecare, division of Ethicon, Inc.). Normal saline solution (0.9% NaCl) was used as the distension medium Administration of antibiotics was not reported
Outcomes	Incidence of de novo adhesions, severity of adhesions according to 1988 AFS classification system and improvement of degree of patency of internal uterine ostium; all outcomes measured after 4 weeks (during early proliferating phase of the following menstrual cycle)
Notes	* Correspondence with authors on 27-12-2014: *1. Which method was used for a statistical power calculation before the trial?* *Our primary outcome was measured by the incidence of de novo IUA. On the basis of data previously published by our group [Guida M, Acunzo G, Di Spiezio Sardo A, Bifulco G, Piccoli R, Pellicano M, Cerrota G, Cirillo D, Nappi C. Effectiveness of auto-cross-linked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic adhesiolysis: a prospective randomized, controlled study. Hum Reprod 2004;19:1461-1464; Acunzo G, Guida M, Pellicano M, Tommaselli GA, Di Spiezio Sardo A, Bifulco G, Cirillo D, Taylor A, Nappi C. Effectiveness of auto-cross-linked hyaluronic acid gel in the prevention of intrauterine adhesions after hysteroscopic adhesiolysis: a prospective randomized, controlled study. Hum Reprod 2003;18:1918-1921], we expected the incidence of adhesions at follow-up in patients undergoing hysteroscopic procedures with the application of the gel to be 10%, and without to be 28%, respectively. These figures are consistent with current literature, which shows a mean incidence of IUA of 25% after common resectoscopic procedures (polypectomy, myomectomy and metroplasty) if adjusted by taking into account that our study was meant to include more adhesiogenic procedures such as endometrial ablation. For the probability of a type 1 statistical error to be less than 0.05, we calculated that a sample of 55 patients per group would provide 80% of statistical power.* *2. Was there any funding for the present study? Was there any conflict of interest?*

	The study was not funded by an external source. All authors had no conflict of interest regarding this study at that time. *3. Is it possible to provide the outcome data of the infertile women included in this study to be able to analyse them on an individual level?* *Unfortunately it is not possible. However the infertile patients were only a small proportion (12 Group 1; 9 Group 2).* *4. Which method was used to conceal the allocation to one of the two interventions?* *The allocation sequence was concealed from the researchers (S.M, B.M, S.M.)* *who enrolled and assessed the participants and attached a sequentially numbered, opaque, sealed and stapled envelope containing the allocated treatment to the clinical record of the patient after having signed the informed consent. The envelope was opened immediately after the surgical removal of the intrauterine removal of the removal of the intrauterine lesion, in order for the surgeon (A.D.S.S.) to either inject the gel (group 1) or not (group 2). Patients were blinded to the procedure until the end of the study. This single-blind study design was adopted to reduce bias derived from the patient's knowledge of which procedure she underwent.* *5. How were the study participants, the treating physicians and the outcome assessors blinded? Who did the outcome assessments? Finally, are you aware of any ongoing research on anti-adhesion therapy following operative hysteroscopy?* *Patients were blinded since they underwent operative hysteroscopy in general anaesthesia or loco-regional anaesthesia (they were awake but couldn't see the monitor) and were kept blinded until the three months follow-up visit. The treating physician (A.D.S.S.) was blinded until removal of the intrauterine lesion or after endometrial ablation, when he was informed whether to inject or not the intrauterine gel. The assessor (M.G.) was blinded since he performed the baseline and the follow-up hysteroscopies and did not participate to the operative hysteroscopies, so he was completely unaware of the allocation of patients. This single-blind study design was adopted to reduce bias derived from the patient's knowledge of which procedure she underwent*

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "After diagnostic hysteroscopy, patients were randomized via computer-generated randomisation list into group 1 (treatment group: operative hysteroscopy plus intrauterine application of Intercoat gel; N = 55) and group 2 (control group: operative hysteroscopy alone; N = 55)" Comment: probably done, as the same team of investigators has published data on a similar randomised trial
Allocation concealment (selection bias)	Low risk	Quote: "The allocation sequence was concealed from the researchers (S.M, B.M, S. M.) who enrolled and assessed the participants and attached a sequentially numbered, opaque, sealed, and stapled envelope containing the allocated treatment to the

		clinical record of the patient after having signed the informed consent" (query clarified by Dr. Attilio DiSpiezio Sardo) Comment: probably done
Blinding of participants and personnel (performance bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome
Blinding of participants and personnel (performance bias) Adhesions	High risk	Quote: "Patients were blinded since they underwent operative hysteroscopy in general anaesthesia or loco-regional anaesthesia (they were awake but couldn't see the monitor) and were kept blinded until the three months follow-up visit" (query clarified by Dr. Attilio DiSpiezio Sardo) Quote: "The envelope was opened immediately after the surgical removal of the intrauterine removal of the removal of the intrauterine lesion, in order for the surgeon (A.D.S.S.) to either inject the gel (group 1) or not (group 2)" (query clarified by Dr. Attilio DiSpiezio Sardo) Comment: personnel not blinded; participants blinded (query clarified by Dr. Attilio DiSpiezio Sardo)
Blinding of outcome assessment (detection bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome
Blinding of outcome assessment (detection bias) Adhesions	Low risk	Quote: "Both the initial and follow-up diagnostic hysteroscopy were performed by the same surgeon (M.G.), who, blinded to patients' randomized allocation, also evaluated the rate and severity of adhesions in each patient" Quote: "The assessor (M.G.) was blinded since he performed the baseline and the follow-up hysteroscopy and did not participate to the operative hysteroscopy, so he was completely unaware of the allocation of patients" (query clarified by Dr. Attilio DiSpiezio Sardo) Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Intention-to-treat was the analysis method used; however, there were no deviations from random allocation"

		Comment: probably done - unlikely to cause attrition bias
Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective outcome reporting when abstract, methods and results were compared
Other bias	Low risk	Comment: no evidence of imbalance in baseline participant characteristics - no co-treatment

Fuchs 2014

Methods	Parallel-group randomised controlled trial Single centre - a gynaecologic endoscopy unit of a tertiary care medical centre in Zerifin, Israel Protocol was approved by the IRB Post hoc statistical power calculation; non-inferiority design No external funding and no conflicts of interest (query clarified by Dr. Moty Pansky)
Participants	Number recruited: 110 women Number excluded before randomisation: 58 women (14 women did not meet inclusion criteria; 37 women declined to participate; 7 women were excluded for other reasons) Number randomly assigned: 52 women Number lost to follow-up: 11 women Number analysed: 41 women Women who underwent hysteroscopic surgery because of suspected retained products of conception between September 2009 and June 2012 were invited to participate in the study, and enrollees gave signed informed consent Inclusion criteria: women 18 to 50 years of age with suspicion of retained products of conception on transvaginal ultrasound, diagnostic office hysteroscopy, or both Study duration: 34 months - between September 2009 and June 2012 Mean age (± SD) in intervention group: 29.5 years (± 5.1 years) Mean age (± SD) in control group: 31.4 years (± 6.5 years) Quote: "The study didn't include women with primary subfertility" (query clarified by Dr. Moty Pansky) Comment: Only women with proven fertility were included in this study
Interventions	Application of Oxiplex gel (N = 21) versus no gel (N = 20) following operative hysteroscopy for retained products of conception All hysteroscopic procedures were performed under general anaesthesia. Pelvic bimanual examination was performed under anaesthesia, and findings were recorded in the medical records. The uterus was considered enlarged when the uterine fundus was palpated above the pelvic brim. Saline solution (NaCl 0.9%) was used as the distension medium. Suspected RPOC was removed via blunt dissection, with a 4-mm loop resectoscope (Stryker Corp., Kalamazoo, MI) as a curette and under direct hysteroscopic view. All specimens were sent for pathological analysis After completion of hysteroscopic dissection, Oxiplex gel was inserted into the uterine cavity of study participants, up to complete filling of the cavity or up to 10 mL gel,

	whichever occurred first. All women were discharged from the hospital several hours after the procedure Both treatment and control groups received sequential hormonal treatment (oestradiol valerate, 2 mg/d, for 11 days, followed by oestradiol valerate, 2 mg/d, and norgestrel, 0. 5 mg/d, for 10 days) and antibiotic therapy (amoxicillin-clavulanic acid, 875 mg, twice daily for 7 days). All women underwent diagnostic office hysteroscopy at 6 to 8 weeks after the operative procedure, performed by a surgeon who was blinded to the treatment group
Outcomes	Intraoperative and postoperative complication rates, incidence of moderate or severe adhesions and pregnancy defined as a positive heartbeat (query clarified by Dr. Moty Pansky) Comment: primary and secondary outcomes not determined
Notes	Quote: "Because this was a pilot study using a non-inferiority design, post hoc power analysis was performed. This calculation showed that the power for detection of a statistically significant difference in rates of intrauterine adhesions between the 2 groups was 24%" Comment: Study was substantially underpowered for the outcome of incidence of moderate or severe intrauterine adhesions * Correspondence with authors on 19-01-2015: *1. The first citation is an interim analysis that included 30 women, and was presented at AAGL on 2011. The second citation is the final analysis that was published in JMIG 2014 and included 52 women. The study population of the second citation includes all 30 women from the first one and 22 additional women.* *2. Allocation was based on a computer-generated randomisation scheme that was prepared in advance by the study coordinator. Sealed envelopes containing allocation were opened only following consent by the treating physician. The study coordinator documented the allocation on a password protected computer.* *3. The control group received NS at the end of the procedure. The participants didn't know which group they were allocated to, nor did the outcome assessors. Naturally, the treating physician at time of procedure was aware of the treatment. Treating physicians' identity was documented and the study coordinator made sure that different physicians performed the treatment and the assessment per patient.* *4. The gel was provided by J&J. There was no funding for the study. There was no conflict of interest.* *5. The study didn't include women with primary subfertility.* *6. This was a pilot study designed to assess safety, hence there was no distinction between primary and secondary outcomes.* *7. Pregnancy was defined as a positive heartbeat.* *8. We are not aware of any ongoing research on anti-adhesion therapy following operative hysteroscopy.*

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	Quote: "The study entrants, in blocks of 12, were randomly allocated via a computer-generated randomisation schedule, using institutional computer software, to treatment with (study group) or without (control group) Oxiplex gel" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "Allocation was based on a computer generated randomisation scheme that was prepared in advance by the study coordinator. Sealed envelopes containing allocation were opened only following consent by the treating physician. The study coordinator documented the allocation on a password protected computer" (query clarified by Dr. Moty Pansky) Comment: probably done
Blinding of participants and personnel (performance bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome
Blinding of participants and personnel (performance bias) Adhesions	High risk	Quote: "Different surgeons performed the operative hysteroscopy and the follow-up diagnostic hysteroscopy. Both the patients and the surgeons who performed the follow-up studies were unaware of patient group assignment" Quote: "The participants didn't know which group they were allocated to, nor did the outcome assessors. Naturally, the treating physician at time of procedure was aware of the treatment. Treating physicians' identity was documented and the study coordinator made sure that different physicians performed the treatment and the assessment per patient" (query clarified by Dr. Moty Pansky) Comment: Participants were probably blinded, as they were under general anaesthesia, but treating physicians were not blinded
Blinding of outcome assessment (detection bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome

Blinding of outcome assessment (detection bias) Adhesions	Low risk	Quote: "Different surgeons performed the operative hysteroscopy and the follow-up diagnostic hysteroscopy" Quote: "All patients underwent diagnostic office hysteroscopy at 6 to 8 weeks after the operative procedure, performed by a surgeon who was blinded to the treatment group" Quote: "The participants didn't know which group they were allocated to, nor did the outcome assessors. Naturally, the treating physician at time of procedure was aware of the treatment. Treating physicians' identity was documented and the study coordinator made sure that different physicians performed the treatment and the assessment per patient" (query clarified by Dr. Moty Pansky) Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote from the Figure 1 CONSORT flow diagram: "In the intervention group five women were excluded from analysis after randomisation: the intervention was discontinued but no further clarification was given" Quote from the Figure 1 CONSORT flow diagram: "In the control group six women were excluded from analysis after randomisation: lost to follow-up (3) and discontinuation of the intervention (3) without further clarification" Comment: likely to cause attrition bias
Selective reporting (reporting bias)	High risk	Comment: At high risk of selective outcome reporting, as live birth rates were not reported for a study from September 2009 to June 2012, and publication of the final study report in 2014
Other bias	High risk	Quote: "Patients with a diagnosis of adhesions (AFS grade 1) were offered an additional procedure for adhesiolysis" Quote: "At follow-up hysteroscopy, 3 patients in the control group (14%) had AFS stage 2 or 3 (moderate to severe) intrauterine adhesions, compared with 1 woman in the study group (4%), who had AFS stage

		3 intrauterine adhesions (P = 0.30) Comment: imbalance between groups for a co-intervention

Guida 2004

Methods	Parallel-group randomised controlled trial after stratification according to type of pathology Single centre - Hysteroscopic Unit of University of Naples "Frederico II" Protocol was approved by the IRB Statistical power calculation for primary outcome of incidence of de novo adhesions (query clarified by Dr. Attilio DiSpiezio Sardo) No external funding and no conflicts of interest (query clarified by Dr. Attilio DiSpiezio Sardo)
Participants	Number recruited: 164 women Number excluded before randomisation: 26 women (18 women refused to undergo operative hysteroscopy; 8 women refused to participate after explanation of the study protocol) Number randomly assigned: 138 women Number lost to follow-up: 6 women Number analysed: 132 women All participants with surgically remediable single lesions (myomas, polyps and uterine septa, subgroups I to III) at diagnostic hysteroscopy were invited to participate in the study Between September 2002 and June 2003, 164 patients met the study's inclusion criteria and were invited to participate in the study. Of these, 26 did not participate in the study: 18 refused to undergo operative hysteroscopy, and 8 refused to participate after explanation of the study protocol Inclusion criteria: hysteroscopic diagnosis of submucous myomas or endometrial polyps or uterine septa Exclusion criteria: age > 50 years, weight > 100 kg, menopausal (FSH > 40 mIU/mL, 17β-oestradiol < 20 pg/mL) or pregnancy (positive β-hCG test), presence of uterovaginal prolapse and severe urinary symptoms, presence of malignancy, presence of severe intercurrent illness (coagulation disorders, systemic disease, severe cardiopathy). Presence of the association of equal or different intrauterine remediable lesions or presence of intrauterine adhesions was also considered an exclusion criterion Study duration: 10 months (between September 2002 and June 2003) Mean age (± SD) in intervention group: 37 years ± 3.2 years Mean age (± SD) in control group: 36 years ± 2.8 years Number of subfertile participants and individual outcome data not available for further IPD analysis (query clarified by Dr. Attilio DiSpiezio Sardo)
Interventions	After diagnostic hysteroscopy and after written consent form was signed, women from each pathology subgroup (submucous myomas, endometrial polyps, septa) were randomly assigned to 2 groups: group A (treatment group) (N = 69) and group B (control group) (N = 69), using a computer-generated randomisation list Treatment group received intrauterine application of 10 mL of ACP gel (Hyalobarrier Gel; Baxter, Pisa, Italy) under hysteroscopic view after operative hysteroscopy

	In control group, hysteroscopic surgery alone was performed Diagnostic hysteroscopy was performed with a 3.5-mm instrument (Gynecare Versascope; Gynecare, Ethicon Inc., Somerville, NJ, USA) and normal saline solution (NaCl 0.9 %) as the distension medium Operative hysteroscopy was performed using a rigid resectoscope (Karl Storz, Tuttlingen, Germany) with a 12-degree fore-oblique telescope with a hook-shaped monopolar electrode Participants from both groups were administered oral antibiotics (cefixime 400 mg/d) (Cefixoral; Menarini, Firenze, Italy) for 3 days after surgery
Outcomes	Incidence of de novo adhesions, mean adhesion score and severity of adhesions according to 1988 AFS classification system; all outcomes measured after 3 months
Notes	* Correspondence with authors on 27-12-2014: *1. Which method was used for a statistical power calculation before the trial?* *Primary outcome was the incidence of adhesion formation at three month follow-up in the two groups (hysteroscopy plus gel vs. hysteroscopy only). We assumed that difference between the two groups in term of de novo intrauterine adhesion formation would be 15% with an incidence of de novo adhesion formation in the hysteroscopy only group of 25% (Taskin et al. J Am Assoc Gynecol Laparosc 2000; 7: 351-354). For the probability of a type I error to be less than .05, we calculated that a sample of 136 patients (68 per group) would provide 80% statistical power. In the study, 138 patients were enrolled and unfortunately, 6 dropped out, leaving 67 patients in the hysteroscopy plus gel group and 65 in the hysteroscopy only group. For this reason, 80% power of the study using the per-protocol sample size analysis was not reached. Nevertheless, the post-hoc power analysis revealed that the study reached an 80% power.* *2. Was there any funding for the present study? Was there any conflict of interest?* *The study was not funded by an external source. All authors had no conflict of interest regarding this study at that time.* *3. Is it possible to provide the outcome data of the infertile women included in this study to be able to analyse them separately?* *Unfortunately it is not possible.* *4. Which method was used to conceal the allocation to one of the two interventions?* *The allocation sequence was concealed from the researchers (G.A., G.B., R.P., M.P.), who enrolled and assessed the participants and attached a sequentially numbered, opaque, sealed, and stapled envelope containing the allocated treatment to the clinical record of the patient after having signed the informed consent. The envelope was opened immediately after the surgical removal of the intrauterine removal of the removal of the intrauterine lesion, in order for the surgeon (M.G.) to either inject the gel (group A) or not (group B). Patients were blinded to the procedure until the end of the study. This single-blind study design was adopted to reduce bias derived from the patient's knowledge of which procedure she underwent.* *5. How were the outcome assessors blinded? Finally, are you aware of any ongoing research on anti-adhesion therapy following operative hysteroscopy?* *The researcher who assessed the de novo formation of intrauterine adhesion (G.A.) was the one who performed the baseline diagnostic hysteroscopy and, successively, performed the 3 month follow-up hysteroscopy. He did not participate to any of the operative hysteroscopies, when the patients were allocated to group A or B and, thus, he was completely unaware to which group the patients were allocated.* *We are not aware of any ongoing research on anti-adhesion therapy following operative*

Guida 2004 (*Continued*)

	hysteroscopy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "After diagnostic hysteroscopy and after the written consent form was signed, patients from each pathology subgroup (submucous myomas, endometrial polyps, septa) were randomized into two groups, group A (treatment group) (N = 69) and group B (control group) (N = 69), using a computer-generated randomisation list" Comment: probably done, as the same team of investigators published data on a similar randomised trial
Allocation concealment (selection bias)	Low risk	Quote: "The allocation sequence was concealed from the researchers (G.A., G.B., R. P., M.P.), who enrolled and assessed the participants and attached a sequentially numbered, opaque, sealed, and stapled envelope containing the allocated treatment to the clinical record of the patient after having signed the informed consent" (query clarified by Dr. Attilio DiSpiezio Sardo) Comment: probably done
Blinding of participants and personnel (performance bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome
Blinding of participants and personnel (performance bias) Adhesions	High risk	Quote: "The envelope was opened immediately after the surgical removal of the intrauterine removal of the removal of the intrauterine lesion, in order for the surgeon (M.G.) to either inject the gel (group A) or not (group B). Patients were blinded to the procedure until the end of the study. This single blind study design was adopted to reduce bias derived from the patient's knowledge of which procedure she underwent" (query clarified by Dr. Attilio DiSpiezio Sardo) Comment: personnel not blinded; participants blinded

Blinding of outcome assessment (detection bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome
Blinding of outcome assessment (detection bias) Adhesions	Low risk	Quote: "Both the initial diagnostic hysteroscopy and the follow-up diagnostic hysteroscopy were performed by the same operator (G.A.). G.A. evaluated the adhesion score for each patient and was blind for patients' randomized allocation, whilst operative hysteroscopies and application of ACP gel were performed by a different operator (M.G.)" Quote: "The researcher who assessed the de novo formation of intrauterine adhesion (G.A.) was the one who performed the baseline diagnostic hysteroscopy and, successively, performed the 3 month follow-up hysteroscopy. He did not participate to any of the operative hysteroscopies, when the patients were allocated to group A or B and, thus, he was completely unaware to which group the patients were allocated" (query clarified by Dr. Attilio DiSpiezio Sardo) Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Six women (two from group A and four from group B) did not attend for follow-up hysteroscopy" Comment: unlikely to cause substantial attrition bias
Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective outcome reporting when abstract, methods and results were compared
Other bias	Low risk	Comment: no evidence of imbalance in baseline participant characteristics - no co-treatment

Lin 2013

Methods	Parallel-group randomised controlled trial Single centre - Reproductive Medicine Centre at Zheijang University, Hangzhou, China Protocol approved by IRB of the Sir Run Run Shaw Hospital, Hangzhou, China, January 2013 Statistical power calculation: not reported Governmental funding by Health Bureau of Zhejiang Province, China
Participants	Number recruited: 207 women Number excluded before randomisation: 6 women Number randomly assigned: 201 women Number lost to follow-up: 39 women Number analysed: 162 women Woman with confirmed IUAs of moderate or severe degree by hysteroscopic examination and history review for the first time in Sir Run Run Shaw Hospital were recruited. All participants were younger than 40 years of age and were trying to conceive Inclusion criteria • Women with confirmed uterine adhesions of moderate or severe degree (AFS score range ≥ 5) by hysteroscopic examination • Participants should be ≥ 18 years of age and < 40 years old, having future pregnancy wish Exclusion criteria • Women > 40 years of age • AFS score < 5 • Do not wish to conceive • Underwent hysteroscopic adhesiolysis before • Cannot follow up study protocol Study duration: 21 months (from 30 January 2013 until 31 October 2014) Age, parity, menstrual characteristics and AFS score before surgery comparable between groups Mean age (± SD) in balloon group: 30 years ± 4.3 years Mean age (± SD) in IUD group: 30 years ± 5.1 years Proportions of subfertile women: 26% in balloon group and 22% in IUD group
Interventions	In all cases, hysteroscopy was carried out by 2 reproductive surgeons with general anaesthesia to confirm the presence of IUAs. Only cases with AFS score ≥ 5 were eligible. A 4.5-mm hysteroscope (Storz, Germany) was used in each case. Adhesions were divided with the use of hysteroscopic scissors. Procedures were carried out under ultrasound or laparoscopic guidance when necessary At the end of the procedure, participants were allocated to 1 of 2 groups according to a randomisation table • Fitting of an IUD (copper coil, Yandai Contraceptive Instrument Company, China) • Fitting of a specially designed intrauterine balloon (Cook Medical Company, Australia) In all cases, hormonal therapy was started shortly after the operation, consisting of oestradiol valerate at a dose of 6 mg per day for 21 to 28 days, with the addition of medroxyprogesterone acetate at a dose of 6 mg per day for the last 7 to 10 days of oestrogen therapy. All devices inserted will be removed in 7 days. Following withdrawal bleed, hormonal therapy was repeated for another cycle

	Second-look hysteroscopy was carried out in the early proliferating phase, 1 to 2 months after the initial operation, assessing adhesion score by AFS criteria. If recurrence of intrauterine adhesions was confirmed at second-look hysteroscopy, a repeat adhesiolysis procedure was performed
Outcomes	Primary outcomes • Severity and extent of intrauterine adhesions were scored according to a classification system recommended by the American Fertility Society (AFS) (1988 version). Score of 1 to 4 was considered to represent mild adhesions, score of 5 to 8 was considered to represent moderate adhesions and score of 9 to 12 represented severe adhesions Secondary outcomes • Pregnancy rates in both groups after surgery
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "After the completion of hysteroscopic adhesiolysis, recruited patients were randomized to one of the two treatment groups by computer-generated numbers" Comment: probably done
Allocation concealment (selection bias)	Unclear risk	Comment: method not stated
Blinding of participants and personnel (performance bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome
Blinding of participants and personnel (performance bias) Adhesions	High risk	Quote: "The surgeon who later performed the second-look hysteroscopy was blinded to the randomisation" Comment: blinding of participants not stated - probably not done
Blinding of outcome assessment (detection bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome
Blinding of outcome assessment (detection bias) Adhesions	Low risk	Quote: "The surgeon who later performed the second-look hysteroscopy was blinded to the randomisation" Comment: probably done

Lin 2013 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Among the 201 subjects randomised, 99 were in the balloon group, and 102 in the IUD group. There were 39 women who were subsequently excluded from the study for the following reasons" Comment: high rate of participant loss to follow-up (39/201, or 19%)
Selective reporting (reporting bias)	High risk	Quote from the study protocol: "Secondary outcomes: pregnancy rates in both groups after surgery" Comment: no pregnancy rates reported in the published article
Other bias	Unclear risk	Co-treatment with repeat adhesiolysis for recurrent or de novo IUAs at second-look hysteroscopy: proportion of cases co-treated with repeat adhesiolysis among comparison groups unknown

Lin 2015

Methods	Parallel-group randomised controlled trial Single centre - tertiary medical centre, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan Study was approved by the IRB Study protocol was registered as NCT01167296 in ClinicalTrials.gov Statistical power calculation was done before start of the trial No conflicts of interest declared by any study authors External funding not reported
Participants	Number recruited: 68 women Number excluded before randomisation: 6 women (5 women refused to participate; 1 woman had a history of PID) Number randomly assigned: 62 women Number lost to follow-up: 2 women Number analysed: 60 women Women 20 to 45 years old undergoing hysteroscopic surgery were eligible for enrolment Exclusion criteria: history of pelvic inflammatory disease (PID), evidence of PID or vaginitis Study duration: 8 months; trial recruited from July 2010 to April 2011 at Shin Kong Wu Ho-Su Memorial Hospital Mean age (± SD) in intervention groupC: 33.4 years (± 4.8 years) Mean age (± SD) in control group: 35.4 years (± 7.2 years) Not clear whether participants suffered from subfertility, and if so, how many (query not clarified by study authors)

Interventions	Randomisation was based on a 1:1 computer-generated scheme in balanced blocks of 4. Randomisation codes were sealed in sequentially numbered opaque envelopes by study co-ordinator. Immediately before surgery, co-ordinator opened the envelope and assigned participants to receive balloon uterine stent insertion (stent group) (N = 31) or not (control group) (N = 31). Women assigned to stent group had balloon uterine stent present for a total of 30 days after surgery. Endometrium was swabbed before and 30 days after surgery, and stent was removed and sent for bacterial culture. For women in the control group, endometrial swabbing was done before and 30 days after surgery as well, but no stent was inserted. Co-ordinator, participants and gynaecologists were not blinded to intervention after assignment Per routine practice, women self administered 400 μg misoprostol (Cytotec; Pharmacia) into the vagina 24 hours and 12 hours before surgery to prime the cervix. After anaesthesia, perineum and vagina were disinfected and draped. Cervix and vagina were subsequently thoroughly disinfected with povidone-iodine, as in vaginal surgery. An applicator swab (Copan Venturi Transystem; Copan Italia) was then inserted into the uterine cavity, with care taken to avoid contact with the vaginal wall. Whole endometrium swabbed from fundus to cervix. Applicator swab placed in a transport tube and sent to laboratory immediately for bacterial culture Operative hysteroscopies performed with use of a 22-F resectoscope (Karl Storz) and 5% glucose solution for uterine distension and irrigation. For women in the stent group, the stent was inserted into the uterine cavity at the conclusion of hysteroscopy, and the balloon inflated with 8 mL sterile water. Postoperatively, women were prescribed 3 days of diclofenac (Cataflam; Novartis Farma) for pain relief. Prophylactic antibiotics were not given. One surgeon (Y.-H.L.) performed all operative procedures and swabbing. Women were instructed to return if any symptoms of PID developed 30 days after surgery, all participants returned to the hospital for bacterial culture and second-look hysteroscopy. After disinfection of the vagina and cervix with povidone-iodine, the endometrium was swabbed, as previously described. For stent group participants, after the balloon was deflated, the stent was removed carefully without touching the vaginal wall. The balloon was cut from the stem and was placed in a sterile jar. Then the endometrium was swabbed as previously described, and balloon and swab were sent to the laboratory immediately for bacterial culture. After cultures were collected, all participants underwent second-look hysteroscopy for assessment of the endometrium
Outcomes	Primary outcome: incidence of bacterial colonisation of the uterus Secondary outcomes: pain intensity on VAS scale used to record worst pain score from 3 days to 30 days following surgery; species of colonising bacteria
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was based on a 1: 1 computer generated scheme in balanced blocks of four"

		Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "Randomization codes were sealed in sequentially numbered opaque envelopes by the study coordinator" Comment: probably done
Blinding of participants and personnel (performance bias) Live birth, pregnancy or miscarriage	Low risk	Quote: "The coordinator, patients, and gynaecologists were not blinded to intervention after assignment" Comment: unequivocal outcome
Blinding of participants and personnel (performance bias) Adhesions	High risk	Quote: "The coordinator, patients, and gynaecologists were not blinded to intervention after assignment" Comment: no blinding of participants, personnel and outcome assessors
Blinding of outcome assessment (detection bias) Live birth, pregnancy or miscarriage	Low risk	Quote: "The coordinator, patients, and gynaecologists were not blinded to intervention after assignment" Comment: unequivocal outcome
Blinding of outcome assessment (detection bias) Adhesions	High risk	Quote: "The coordinator, patients, and gynaecologists were not blinded to intervention after assignment" Comment: no blinding of participants, personnel and outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "A total of 62 women were included in the study, and 31 women were assigned to each group. The balloon uterine stent fell out after a week in one woman in the stent group, and one woman in the control group was lost to follow-up. Both of these patients were excluded from analysis. Data for 60 women were analysed" Comment: unlikely to cause substantial attrition bias
Selective reporting (reporting bias)	Unclear risk	Quote: "Main outcome measure(s): The primary outcome was the incidence of bacterial colonization of the uterus. Secondary outcomes were pain intensity and species of colonizing bacteria" Quote: "All second-look hysteroscopies revealed a normal endometrium. No woman had IUAs" Comment: According to registered proto-

		col, predefined outcomes were as follows • Primary outcome measures: intrauterine bacteria count • Secondary outcome measures: intrauterine adhesion Published report states in results section that no participant had IUAs at second-look hysteroscopy, but this important finding is not explicitly stated in the abstract
Other bias	High risk	Number of participants with IUAs was twice as high in the intervention group (17/31) vs the control group (10/31) Comment: imbalance in baseline characteristics between comparison groups

Roy 2014

Methods	Parallel-group randomised controlled trial Single centre - Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India Protocol was approved by the IRB No statistical power calculation (query clarified by Dr. Murali Subbaiah) No funding (query clarified by Dr. Murali Subbaiah) No conflict of interest (query clarified by Dr. Murali Subbaiah)
Participants	Number recruited: 100 women Number excluded before randomisation: 10 women Number randomly assigned: 90 women Number lost to follow-up: 5 women did not attend for second-look hysteroscopy and were excluded from analysis of second-look hysteroscopy findings; 2 women did attend for second-look hysteroscopy but were lost to follow-up for assessment of reproductive outcome Number analysed: 85 women for second-look hysteroscopy findings; 83 women for reproductive outcomes Women with septate uterus with history of miscarriage or subfertility were included in the study. All subfertile women underwent diagnostic laparoscopy to rule out other causes of subfertility Other inclusion criteria: hysteroscopic diagnosis of uterine septa; negative result of urine pregnancy test; written informed consent Exclusion criteria: age > 35 years; acute cervicitis; presence of any other known cause of infertility or abortion 90 original participants were 20 to 35 years of age and had a history of infertility (N = 31) or abortion (N = 59); of these, 40 had first-trimester and 19 had second-trimester spontaneous abortions Study duration: 12 months; this randomised, placebo-controlled study was conducted over a period of 1 year from January 2011 to December 2011 Mean duration of infertility (± SD) in intervention group: 5.9 years (± 1.8 years)

	Mean age (± SD) in intervention group: 28.7 years (± 4.8 years) Mean duration of infertility (± SD) in control group: 6.2 years (± 1.1 years) Mean age (± SD) in control group: 27.3 years (± 3.9 years) Comment: mixed population of primary/secondary subfertility and miscarriage. This was clarified by Dr. Murali Subbaiah, quoting: "only 30 infertile patients were included - the rest had abortions"
Interventions	Oestrogen therapy (N = 42) vs placebo (N = 43) during 30 days Hysteroscopic resection of septum performed under general anaesthesia by a single operator in the early proliferating phase of the menstrual cycle. Operative hysteroscopy performed by means of a rigid resectoscope (Karl Storz Endoskope, Germany) with a 30-degree telescope, equipped with a hysteroscopic monopolar (Collin's) knife. Cutting current was set at 60 watts. After 10-mm cervical dilation was achieved using Hegar's dilator, uterine cavity was distended by means of glycine solution (1.5%) After septal resection, treatment group received 2 mg oestradiol valerate, once daily for 30 days; in the control group, folic acid tablet (5 mg) was given as a placebo for 30 days Second-look hysteroscopy was performed by the same operator after 2 months to check for a residual septum and uterine cavity adhesions. This was performed as an outpatient procedure with a 4-mm, 30°-angled lens
Outcomes	Intrauterine adhesions at second-look hysteroscopy after 2 months, classified according to American Fertility Society classification; remnant septum defined as septum longer than 1 cm at second-look hysteroscopy after 2 months; pregnancy, ongoing pregnancy and miscarriage measured after contact by telephone on a 3-month basis during 12- to 24-month period of follow-up
Notes	Answers to queries on 06-12-2014: *Respected Sir,* *I would like to apologize for the delay in response. This was a small study and only 30 infertile patients were included (The rest had abortions). Fertility outcome after septal resection in infertile women was not separately analysed (Numbers are too small and the period of follow up is also less). Power calculation was not done for this study.* *There was no funding or conflict of interest.* *The two groups were coded as A and B and were concealed in separate covers. A third person who was not involved in the study was asked to choose one of the concealed covers randomly, and this was assigned. The investigators and patients were blinded to treatment allotment.* *I am not aware of any ongoing research on anti-adhesion therapy following operative hysteroscopy.* *Yours sincerely,* *Dr. Murali Subbaiah*

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "They were prospectively randomized into two groups, group A (treatment group) (*N* = 45) and group B (control group) (*N* = 45), using a computer-gener-

		ated randomisation list" Comment: probably done
Allocation concealment (selection bias)	Low risk	Quote: "The investigators and patients were blinded to treatment allotment" Comment: method clarified by Dr. Murali Subbaiah, quoting: "The two groups were coded as A and B and were concealed in separate covers. A third person who was not involved in the study was asked to choose one of the concealed covers randomly, and this was assigned. The investigators and patients were blinded to treatment allotment"
Blinding of participants and personnel (performance bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome
Blinding of participants and personnel (performance bias) Adhesions	Low risk	Quote: "The investigators and patients were blinded to treatment allotment" Quote: "After septal resection, the treatment group received 2 mg of oestradiol valerate, once daily for 30 days; in the control group, folic acid tablet (5 mg) was given as a placebo for 30 days" Comment: probably done
Blinding of outcome assessment (detection bias) Live birth, pregnancy or miscarriage	Low risk	Comment: unequivocal outcome
Blinding of outcome assessment (detection bias) Adhesions	Low risk	Quote: "The investigators and patients were blinded to treatment allotment" Quote: "After septal resection, the treatment group received 2 mg of oestradiol valerate, once daily for 30 days; in the control group, folic acid tablet (5 mg) was given as a placebo for 30 days" Comment: probably done
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Five women (three from group A and two from group B) did not attend for follow-up hysteroscopy and were excluded from the study. Further, two patients (one from each group) were lost to follow up" Comment: no intention-to-treat analysis, but numbers of women excluded after randomisation or lost to follow-up and reasons were balanced between comparison groups

Roy 2014 (*Continued*)

Selective reporting (reporting bias)	Low risk	Comment: no evidence of selective reporting
Other bias	Low risk	No evidence of baseline imbalance

Abbreviations:
ACP: Auto-cross-linked polysaccharide.
ART: Assisted reproductive technology.
ASRM: American Society for Reproductive Medicine.
β-hCG: Beta-human chorionic gonadotropin.
FSH: Follicle-stimulating hormone.
HSG: Hysterosalpingography.
IPD: Individual patient data.
IRB: Institutional review board.
ITT: Intention-to-treat.
PID: Pelvic inflammatory disease.
RPOC: Retained products of conception.
SD: Standard deviation.
VAS: Visual analogue scale.

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

Study	Reason for exclusion
Bednarek 2011	Quote: "We performed a randomised non-inferiority trial involving women undergoing uterine aspiration for induced or spontaneous abortion at 5 to 12 weeks of gestation who desired an IUD. Subjects were randomly assigned (in a 5:6 ratio) to IUD insertion immediately after the procedure or 2 to 6 weeks afterward (delayed insertion). The primary outcome was the rate of IUD expulsion 6 months after IUD insertion" Comment: not answering PICO research question
Hooker 2011	Quote: "Consented patients, who had at least one previous suction or abrasive (blunt or sharp) curettage for a miscarriage in the history, visiting the outpatient clinic with a miscarriage and planned for curettage, will be included in the study. The ultrasound is a key in the diagnosis of miscarriage; at least one recent ultrasound examination (made within 7 days before randomisation) is required for inclusion. The maximum gestational age at inclusion is 14 weeks" Comment: not answering PICO research question
Hu 2014a	Intervention: hysteroscopic adhesiolysis followed by collagen scaffold loaded with autologous bone marrow stem cell treatment. Study design: observational; case series Comment: observational study
Hu 2014b	Intervention: hysteroscopic adhesiolysis followed by collagen scaffold loaded with umbilical cord blood-derived mesenchymal stem cell treatment. Study design: observational; case series Comment: observational study

(*Continued*)

Johns 2001	Quote: "OBJECTIVE: To assess the safety and efficacy of the Intergel adhesion prevention solution, a 0.5% ferric hyaluronate gel, in reducing adhesions in patients undergoing peritoneal cavity surgery by laparotomy with a planned second-look laparoscopy. DESIGN: Randomized, third-party blinded, placebo-controlled, parallel group. SETTING: Eleven centres in the United States, and five centres in Europe. PATIENT(S): Women aged 18-46 years who wanted to retain their fertility. INTERVENTION(S): Patients received 300 mL of Intergel solution (N = 143) or lactated Ringer's solution (N = 138) as an intraperitoneal instillate at the completion of surgery. MAIN OUTCOME MEASURE(S): At second-look laparoscopy 6-12 weeks later, the presence of adhesions was evaluated at 24 abdominal sites" Comment: not answering PICO research question
Kim 2012	Quote: "The exclusion criteria were women who planned to use an intrauterine device for contraception during the study period; (...); women who were pregnant or who planned pregnancy during the study period (...)" Comment: excluded women with subfertility
Kurtz 2002	Quote: "This randomised controlled blind prospective study is undertaken to evaluate the safety and efficacy of Seprafilm™ - a novel bioresorbable membrane of chemically modified hyaluronic acid and carboxymethylcellulose - in prevention and reduction of postoperative endometrial and endocervical synechiae formation after general suction evacuation or curettage for incomplete, missed, and recurrent abortion" Comment: not answering PICO research question
Letouzey 2014	Quote: "The main objective of this study is to describe the level of expression of the biological factors involved in the formation of adhesions (Transforming growth factor beta, Activin A, inhibin) at the time of a first diagnostic hysteroscopy among women with synechia, another intracavitary disease or no intracavitary disease"; "Study design: observational model: cohort; time perspective: prospective" Comment: observational study
Pabuccu 2008	Quote: "We randomized patients sequentially, according to their entry into the study, after the study started" Comment: quasi-randomised study
Tonguc 2010	Quote: "A statistician allotted the participants to their postsurgical treatment groups according to their application numbers" Comment: quasi-randomised study
Tsapanos 2002	Quote: "This randomised controlled blind prospective study is undertaken to evaluate the safety and efficacy of Seprafilm™ - a novel bioresorbable membrane of chemically modified hyaluronic acid and carboxymethylcellulose - in prevention and reduction of postoperative endometrial and endocervical synechiae formation after general suction evacuation or curettage for incomplete, missed, and recurrent abortion" Quote: "Endometrial synechiae formation was evaluated with the use of hysterosalpingography (HSG) in patients of all groups without pregnancy success 8 months after the intervention" Comment: not answering PICO research question
Yaar 2004	Quote: "OBJECTIVE: To evaluate the role of prophylactic estrogen administration on preventing intrauterine adhesion formation following D&C" Comment: not answering PICO research question

Abbreviations:
IUD: Intrauterine device.

PICO: Population, intervention, comparator, outcome

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

Paz 2012

Trial name or title	Efficiency of INTERCOAT (Oxiplex/AP Gel) in Preventing Intrauterine Adhesion Formation in Hysteroscopic Surgery
Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: double-blind (participant, caregiver) Primary purpose: prevention
Participants	Women 18 to 50 years of age Inclusion criteria • Between 18 and 50 years of age • Must be able to understand, read and sign consent form Exclusion criteria • Signs of infection upon admission • Ongoing pregnancy • Carcinoma of the uterus or cervix • Recurrent PID • Women admitted for endometrial ablation • Women who gave birth 6 weeks ago • Women participating in another study
Interventions	• Intervention: injection of Intercoat into the uterine cavity at the end of hysteroscopy • Control: no injection of Intercoat
Outcomes	Not provided
Starting date	December 2012
Contact information	Moran Paz, MD Carmel Medical Center, Israel Telephone: 972-4-8250637 e-mail: MORANPA@CLALIT.GOV.IL
Notes	Status: recruiting (query not answered)

Revel 2011

Trial name or title	Safety Study of Use of Hyaluronic Acid Gel to Prevent Intrauterine Adhesions in Hysteroscopic Surgery
Methods	Allocation: randomised Endpoint classification: safety study Intervention model: parallel assignment

	Masking: single-blind (participant) Primary purpose: prevention
Participants	Inclusion criteria • 18 years of age and over • Need of hysteroscopic surgery Exclusion criteria • Preoperative fever or infection • Malignancy • Previous PID • Contraindications for anaesthesia • Pregnancy • Younger than 18 years of age • Not able to read and/or understand informed consent • Taking medicine other than oral contraceptives
Interventions	• Intervention: use of hyaluronic acid gel • Control: no hyaluronic acid gel
Outcomes	Primary outcome: participant satisfaction following gel application
Starting date	November 2011
Contact information	Ariel Revel, MD Hadassah Medical Organization, Israel Telephone: 97226777111 ext 76389 e-mail: arielr2@hadassah.org.il
Notes	Status: not yet recruiting (query not answered)

DATA AND ANALYSES

Comparison 1. Inserted device vs no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	1	24	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.18, 5.46]
1.1 IU balloon	1	24	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.18, 5.46]
2 Clinical pregnancy	1	24	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.06, 18.08]
2.1 IU balloon	1	24	Odds Ratio (M-H, Random, 95% CI)	1.0 [0.06, 18.08]
3 Miscarriage	1	22	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.11, 4.00]
3.1 IU balloon	1	22	Odds Ratio (M-H, Random, 95% CI)	0.66 [0.11, 4.00]
4 Presence of intrauterine adhesions at second-look hysteroscopy	1	60	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.1 IU balloon	1	60	Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Inserted device vs another inserted device

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Presence of intrauterine adhesions at second-look hysteroscopy	1	162	Odds Ratio (M-H, Random, 95% CI)	1.23 [0.64, 2.37]

Comparison 3. Hormonal treatment vs no treatment or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	1	83	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.37, 2.33]
1.1 Hormonal treatment vs placebo	1	83	Odds Ratio (M-H, Random, 95% CI)	0.93 [0.37, 2.33]
2 Clinical pregnancy	1	83	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.35, 2.06]
2.1 Hormonal treatment vs placebo	1	83	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.35, 2.06]
3 Miscarriage	1	32	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.10, 5.01]
3.1 Hormonal treatment vs placebo	1	32	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.10, 5.01]
4 Presence of intrauterine adhesions at second-look hysteroscopy	1	85	Odds Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.72]

4.1 Hormonal treatment vs placebo	1	85	Odds Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.72]

Comparison 4. Gel vs no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical pregnancy	1	41	Odds Ratio (M-H, Random, 95% CI)	2.83 [0.62, 13.04]
1.1 Poly gel	1	41	Odds Ratio (M-H, Random, 95% CI)	2.83 [0.62, 13.04]
2 Presence of intrauterine adhesions at second-look hysteroscopy	5	383	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.20, 0.67]
2.1 HA gel at 9 to 12 weeks	3	256	Odds Ratio (M-H, Random, 95% CI)	0.41 [0.22, 0.77]
2.2 Poly gel at 0 to 4 weeks	1	86	Odds Ratio (M-H, Random, 95% CI)	0.14 [0.02, 1.21]
2.3 Poly gel at 5 to 8 weeks	1	41	Odds Ratio (M-H, Random, 95% CI)	0.28 [0.03, 2.98]
3 Mean adhesion scores at 12 weeks	2	43	Mean Difference (IV, Random, 95% CI)	-1.90 [-3.21, -0.59]
3.1 in women treated for fibroids	1	12	Mean Difference (IV, Random, 95% CI)	-1.25 [-2.21, -0.29]
3.2 in women treated for polyps	1	8	Mean Difference (IV, Random, 95% CI)	-1.5 [-1.95, -1.05]
3.3 in women treated for uterine septa	1	4	Mean Difference (IV, Random, 95% CI)	-1.33 [-2.65, -0.01]
3.4 in women treated for intrauterine adhesions	1	19	Mean Difference (IV, Random, 95% CI)	-3.3 [-3.43, -3.17]
4 Mild adhesions at second-look hysteroscopy	4	62	Odds Ratio (M-H, Random, 95% CI)	17.22 [4.09, 72.42]
4.1 HA gel at 9 to 12 weeks	3	55	Odds Ratio (M-H, Random, 95% CI)	18.66 [3.92, 88.90]
4.2 Poly gel at 0 to 4 weeks	1	7	Odds Ratio (M-H, Random, 95% CI)	11.00 [0.28, 433.80]
5 Moderate or severe adhesions at second-look hysteroscopy	5	103	Odds Ratio (M-H, Random, 95% CI)	0.09 [0.03, 0.30]
5.1 HA gel at 9 to 12 weeks	3	55	Odds Ratio (M-H, Random, 95% CI)	0.05 [0.01, 0.26]
5.2 Poly gel at 0 to 4 weeks	1	7	Odds Ratio (M-H, Random, 95% CI)	0.09 [0.00, 3.59]
5.3 Poly gel at 5 to 8 weeks	1	41	Odds Ratio (M-H, Random, 95% CI)	0.28 [0.03, 2.98]

Comparison 6. Graft vs no graft

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	1	43	Odds Ratio (M-H, Random, 95% CI)	1.5 [0.14, 15.87]
2 Clinical pregnancy	1	43	Odds Ratio (M-H, Random, 95% CI)	2.29 [0.42, 12.56]
3 Miscarriage	1	10	Odds Ratio (M-H, Random, 95% CI)	1.67 [0.07, 37.73]

Comparison 7. Any therapy vs no treatment or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Live birth	3	150	Odds Ratio (M-H, Random, 95% CI)	0.99 [0.46, 2.13]
2 Clinical pregnancy	4	191	Odds Ratio (M-H, Random, 95% CI)	1.27 [0.65, 2.51]
3 Miscarriage	3	64	Odds Ratio (M-H, Random, 95% CI)	0.78 [0.23, 2.65]
4 Presence of intrauterine adhesions at second-look hysteroscopy	7	528	Odds Ratio (M-H, Random, 95% CI)	0.36 [0.20, 0.64]
4.1 gels	5	383	Odds Ratio (M-H, Random, 95% CI)	0.37 [0.20, 0.67]
4.2 treatment other than gels	2	145	Odds Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.72]
5 Mean adhesion scores	2	43	Mean Difference (IV, Random, 95% CI)	-1.90 [-3.21, -0.59]
5.1 in women treated for fibroids	1	12	Mean Difference (IV, Random, 95% CI)	-1.25 [-2.21, -0.29]
5.2 in women treated for polyps	1	8	Mean Difference (IV, Random, 95% CI)	-1.5 [-1.95, -1.05]
5.3 in women treated for uterine septa	1	4	Mean Difference (IV, Random, 95% CI)	-1.33 [-2.65, -0.01]
5.4 in women treated for intrauterine adhesions	1	19	Mean Difference (IV, Random, 95% CI)	-3.3 [-3.43, -3.17]
6 Mild adhesions at second-look hysteroscopy	4	62	Odds Ratio (M-H, Random, 95% CI)	17.22 [4.09, 72.42]
6.1 HA gel at 9 to 12 weeks	3	55	Odds Ratio (M-H, Random, 95% CI)	18.66 [3.92, 88.90]
6.2 Poly gel at 0 to 4 weeks	1	7	Odds Ratio (M-H, Random, 95% CI)	11.00 [0.28, 433.80]
7 Moderate or severe adhesions at second-look hysteroscopy	5	103	Odds Ratio (M-H, Random, 95% CI)	0.09 [0.03, 0.30]
7.1 HA gel at 9 to 12 weeks	3	55	Odds Ratio (M-H, Random, 95% CI)	0.05 [0.01, 0.26]
7.2 Poly gel at 0 to 4 weeks	1	7	Odds Ratio (M-H, Random, 95% CI)	0.09 [0.00, 3.59]
7.3 Poly gel at 5 to 8 weeks	1	41	Odds Ratio (M-H, Random, 95% CI)	0.28 [0.03, 2.98]

Comparison 8. Any therapy vs any other therapy

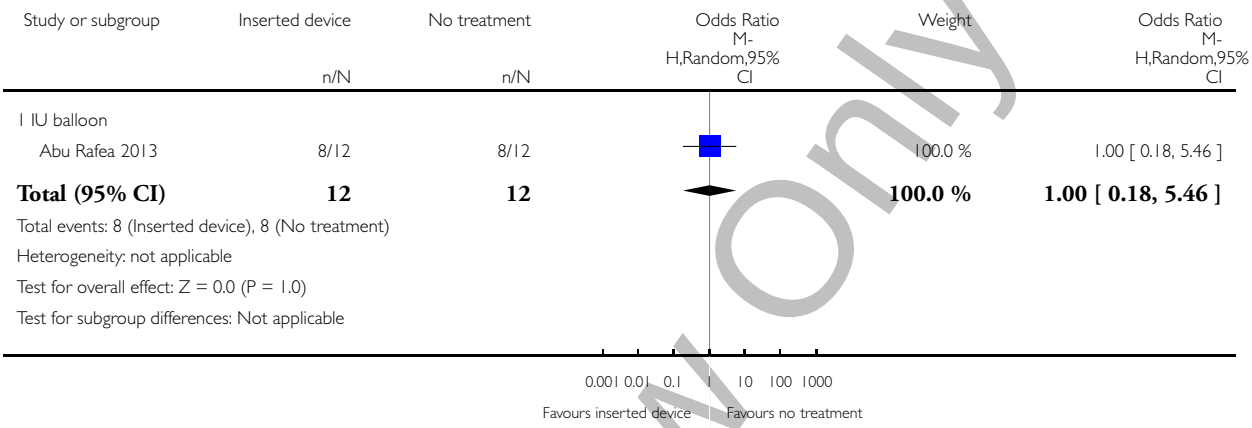
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Presence of intrauterine adhesions at second-look hysteroscopy	1	162	Odds Ratio (M-H, Random, 95% CI)	1.23 [0.64, 2.37]

Analysis 1.1. Comparison 1 Inserted device vs no treatment, Outcome 1 Live birth.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 1 Inserted device vs no treatment

Outcome: 1 Live birth

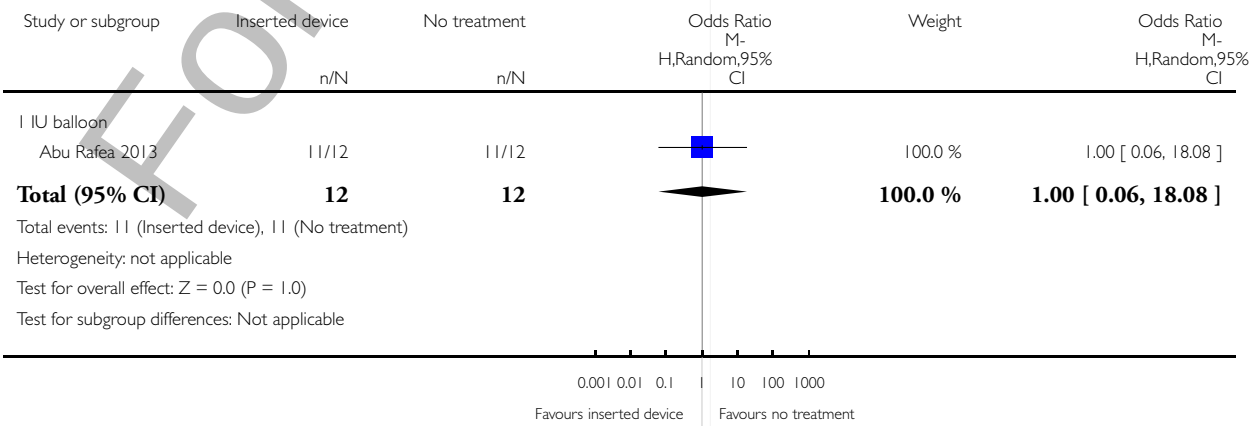


Analysis 1.2. Comparison 1 Inserted device vs no treatment, Outcome 2 Clinical pregnancy.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 1 Inserted device vs no treatment

Outcome: 2 Clinical pregnancy

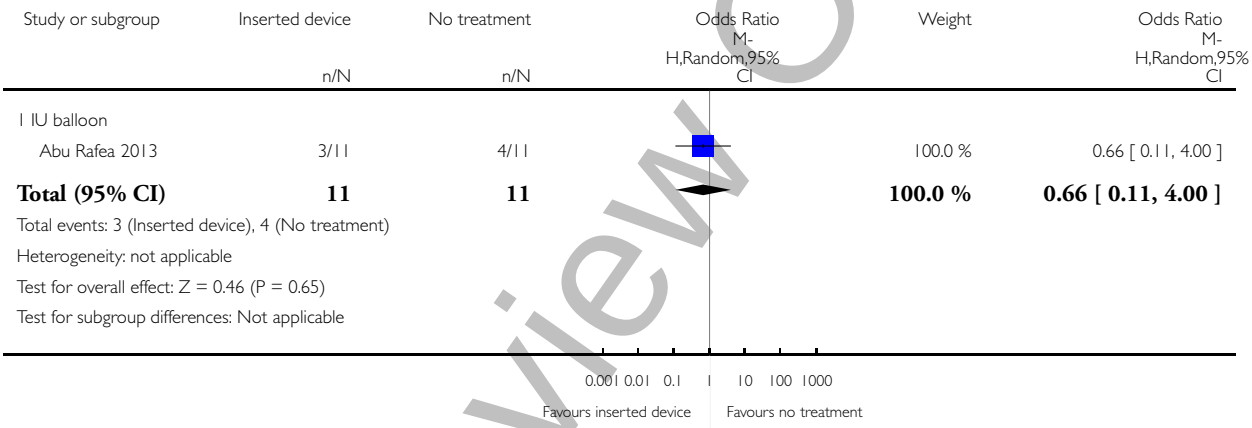


Analysis 1.3. Comparison 1 Inserted device vs no treatment, Outcome 3 Miscarriage.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 1 Inserted device vs no treatment

Outcome: 3 Miscarriage



Analysis 1.4. Comparison 1 Inserted device vs no treatment, Outcome 4 Presence of intrauterine adhesions at second-look hysteroscopy.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 1 Inserted device vs no treatment

Outcome: 4 Presence of intrauterine adhesions at second-look hysteroscopy

Study or subgroup	Inserted device n/N	No treatment n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 IU balloon					
Lin 2015 (1)	0/30	0/30			Not estimable
Total (95% CI)	**30**	**30**			**Not estimable**
Total events: 0 (Inserted device), 0 (No treatment)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%					

(1) It is not clear if and how many participants suffered from subfertility (query not clarified by the study authors).

Analysis 2.1. Comparison 2 Inserted device vs another inserted device, Outcome 1 Presence of intrauterine adhesions at second-look hysteroscopy.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 2 Inserted device vs another inserted device

Outcome: 1 Presence of intrauterine adhesions at second-look hysteroscopy

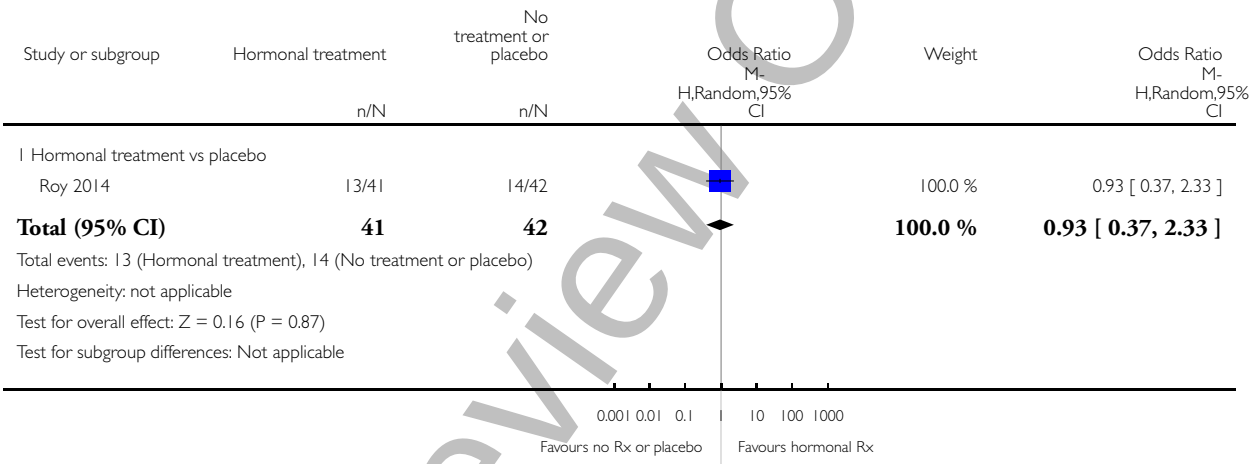
Study or subgroup	IUD n/N	IU balloon n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Lin 2013	28/80	25/82		100.0 %	1.23 [0.64, 2.37]
Total (95% CI)	**80**	**82**		**100.0 %**	**1.23 [0.64, 2.37]**
Total events: 28 (IUD), 25 (IU balloon)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					
Test for subgroup differences: Not applicable					

Analysis 3.1. Comparison 3 Hormonal treatment vs no treatment or placebo, Outcome 1 Live birth.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 3 Hormonal treatment vs no treatment or placebo

Outcome: 1 Live birth



Analysis 3.2. Comparison 3 Hormonal treatment vs no treatment or placebo, Outcome 2 Clinical pregnancy.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 3 Hormonal treatment vs no treatment or placebo

Outcome: 2 Clinical pregnancy

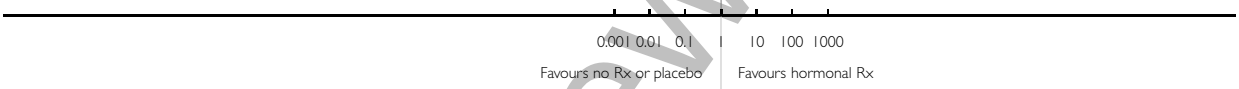
Study or subgroup	Hormonal treatment n/N	No treatment or placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Hormonal treatment vs placebo					
Roy 2014	15/41	17/42		100.0 %	0.85 [0.35, 2.06]
Total (95% CI)	**41**	**42**		**100.0 %**	**0.85 [0.35, 2.06]**

Total events: 15 (Hormonal treatment), 17 (No treatment or placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 0.36 (P = 0.72)

Test for subgroup differences: Not applicable

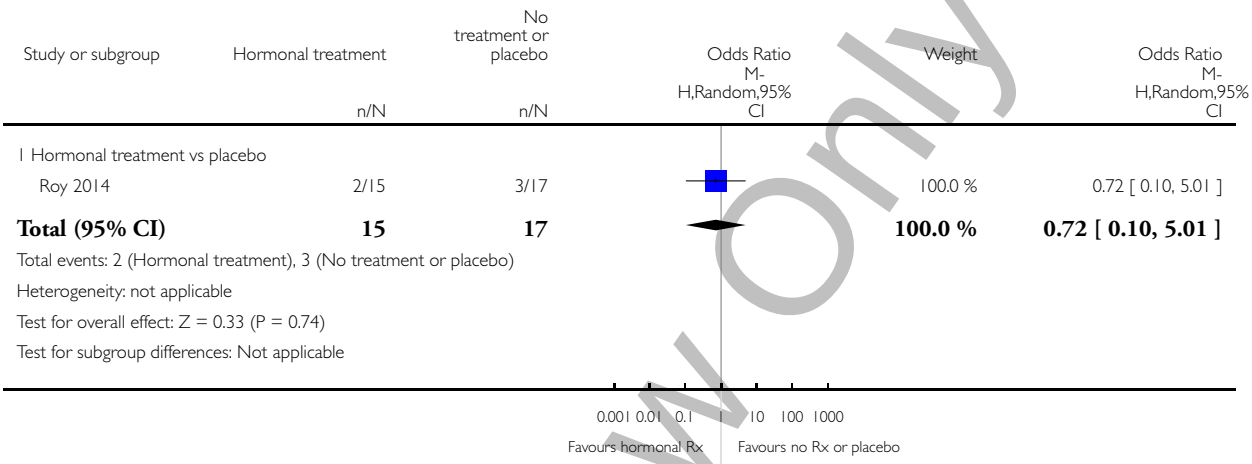


Analysis 3.3. Comparison 3 Hormonal treatment vs no treatment or placebo, Outcome 3 Miscarriage.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 3 Hormonal treatment vs no treatment or placebo

Outcome: 3 Miscarriage



Analysis 3.4. Comparison 3 Hormonal treatment vs no treatment or placebo, Outcome 4 Presence of intrauterine adhesions at second-look hysteroscopy.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 3 Hormonal treatment vs no treatment or placebo

Outcome: 4 Presence of intrauterine adhesions at second-look hysteroscopy

Study or subgroup	Hormonal treatment n/N	No treatment or placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Hormonal treatment vs placebo					
Roy 2014	0/42	3/43		100.0 %	0.14 [0.01, 2.72]
Total (95% CI)	**42**	**43**		**100.0 %**	**0.14 [0.01, 2.72]**

Total events: 0 (Hormonal treatment), 3 (No treatment or placebo)

Heterogeneity: not applicable

Test for overall effect: Z = 1.31 (P = 0.19)

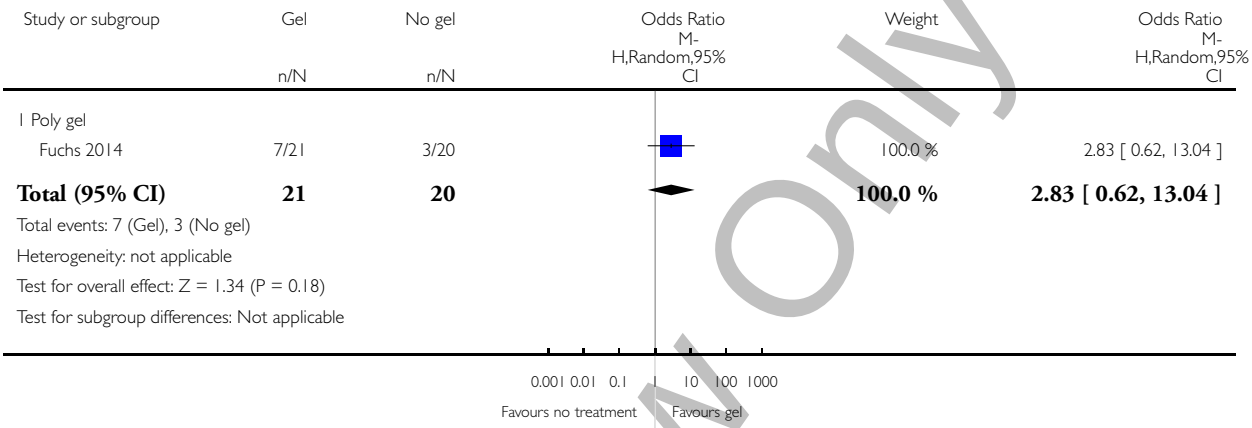
Test for subgroup differences: Not applicable

Analysis 4.1. Comparison 4 Gel vs no treatment, Outcome 1 Clinical pregnancy.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 4 Gel vs no treatment

Outcome: 1 Clinical pregnancy

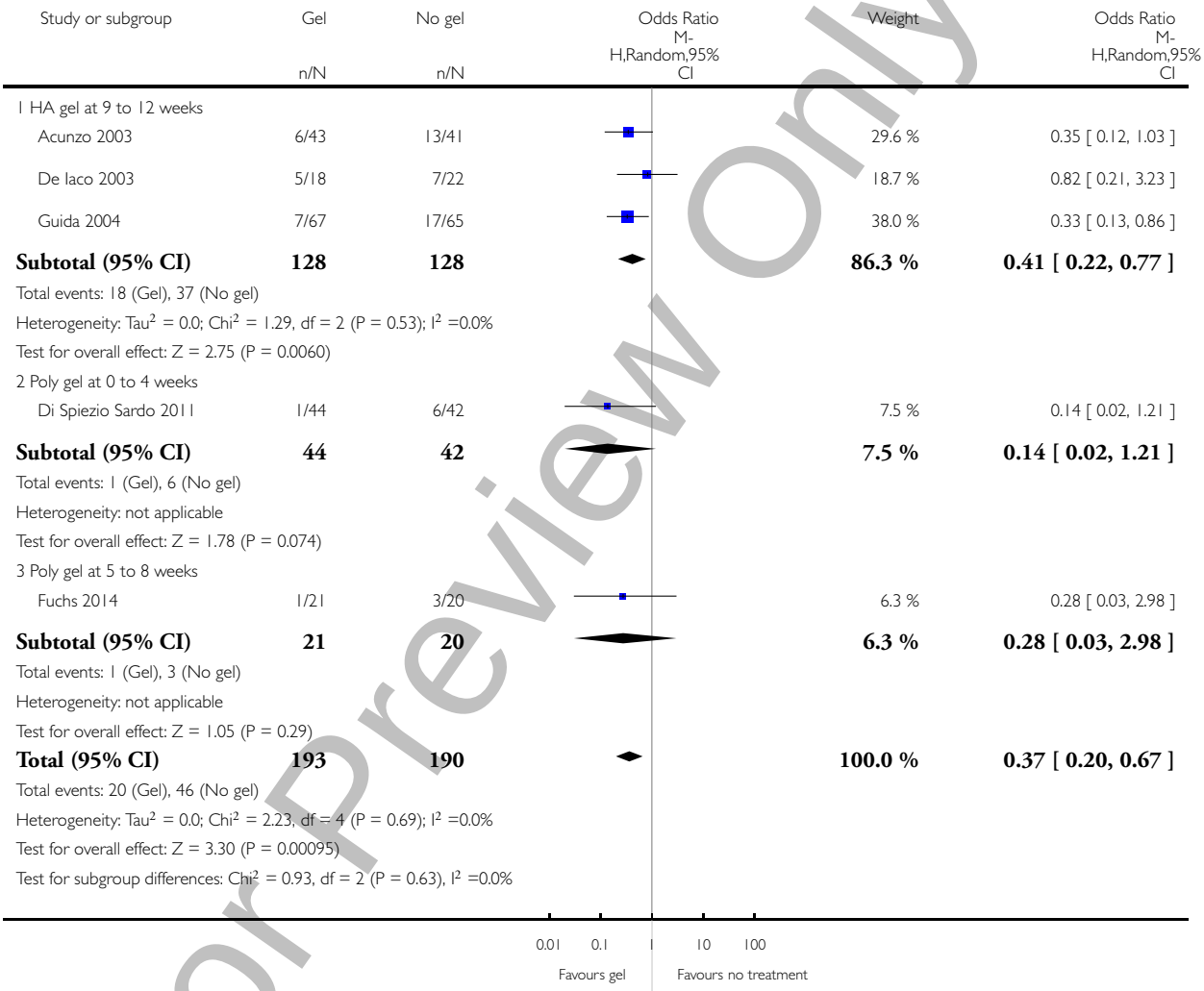


Analysis 4.2. Comparison 4 Gel vs no treatment, Outcome 2 Presence of intrauterine adhesions at second-look hysteroscopy.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 4 Gel vs no treatment

Outcome: 2 Presence of intrauterine adhesions at second-look hysteroscopy



Analysis 4.3. Comparison 4 Gel vs no treatment, Outcome 3 Mean adhesion scores at 12 weeks.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 4 Gel vs no treatment

Outcome: 3 Mean adhesion scores at 12 weeks

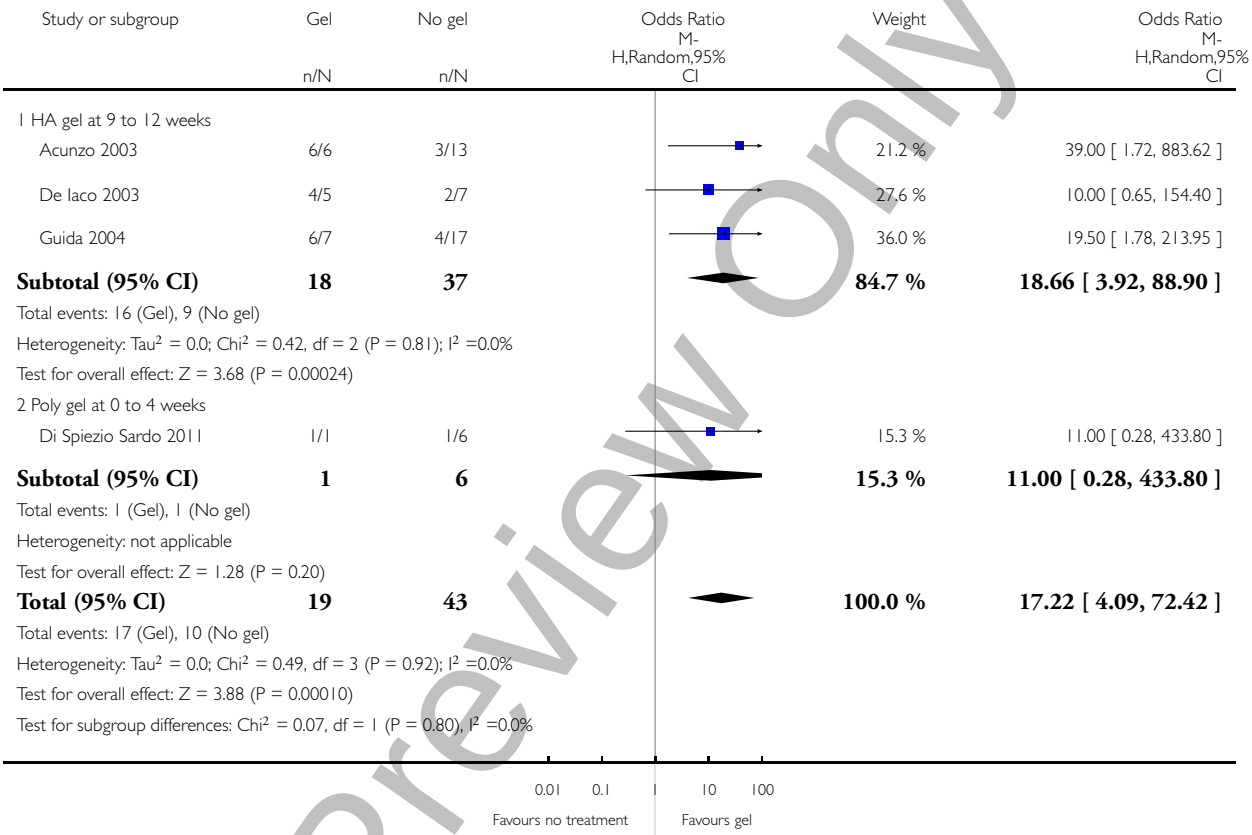
Study or subgroup	Gel N	Mean(SD)	No gel N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 in women treated for fibroids							
Guida 2004	4	2.25 (0.5)	8	3.5 (1.19)		24.1 %	-1.25 [-2.21, -0.29]
Subtotal (95% CI)	**4**		**8**			**24.1 %**	**-1.25 [-2.21, -0.29]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.55 (P = 0.011)							
2 in women treated for polyps							
Guida 2004	2	2 (0.1)	6	3.5 (0.54)		26.7 %	-1.50 [-1.95, -1.05]
Subtotal (95% CI)	**2**		**6**			**26.7 %**	**-1.50 [-1.95, -1.05]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.48 (P < 0.00001)							
3 in women treated for uterine septa							
Guida 2004	1	4 (0.1)	3	5.33 (1.15)		21.6 %	-1.33 [-2.65, -0.01]
Subtotal (95% CI)	**1**		**3**			**21.6 %**	**-1.33 [-2.65, -0.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.98 (P = 0.048)							
4 in women treated for intrauterine adhesions							
Acunzo 2003	6	2 (0.1)	13	5.3 (0.2)		27.6 %	-3.30 [-3.43, -3.17]
Subtotal (95% CI)	**6**		**13**			**27.6 %**	**-3.30 [-3.43, -3.17]**
Heterogeneity: not applicable							
Test for overall effect: Z = 47.91 (P < 0.00001)							
Total (95% CI)	**13**		**30**			**100.0 %**	**-1.90 [-3.21, -0.59]**
Heterogeneity: Tau^2 = 1.62; Chi^2 = 77.43, df = 3 (P<0.00001); I^2 =96%							
Test for overall effect: Z = 2.84 (P = 0.0046)							
Test for subgroup differences: Chi^2 = 77.43, df = 3 (P = 0.00), I^2 =96%							

Analysis 4.4. Comparison 4 Gel vs no treatment, Outcome 4 Mild adhesions at second-look hysteroscopy.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 4 Gel vs no treatment

Outcome: 4 Mild adhesions at second-look hysteroscopy

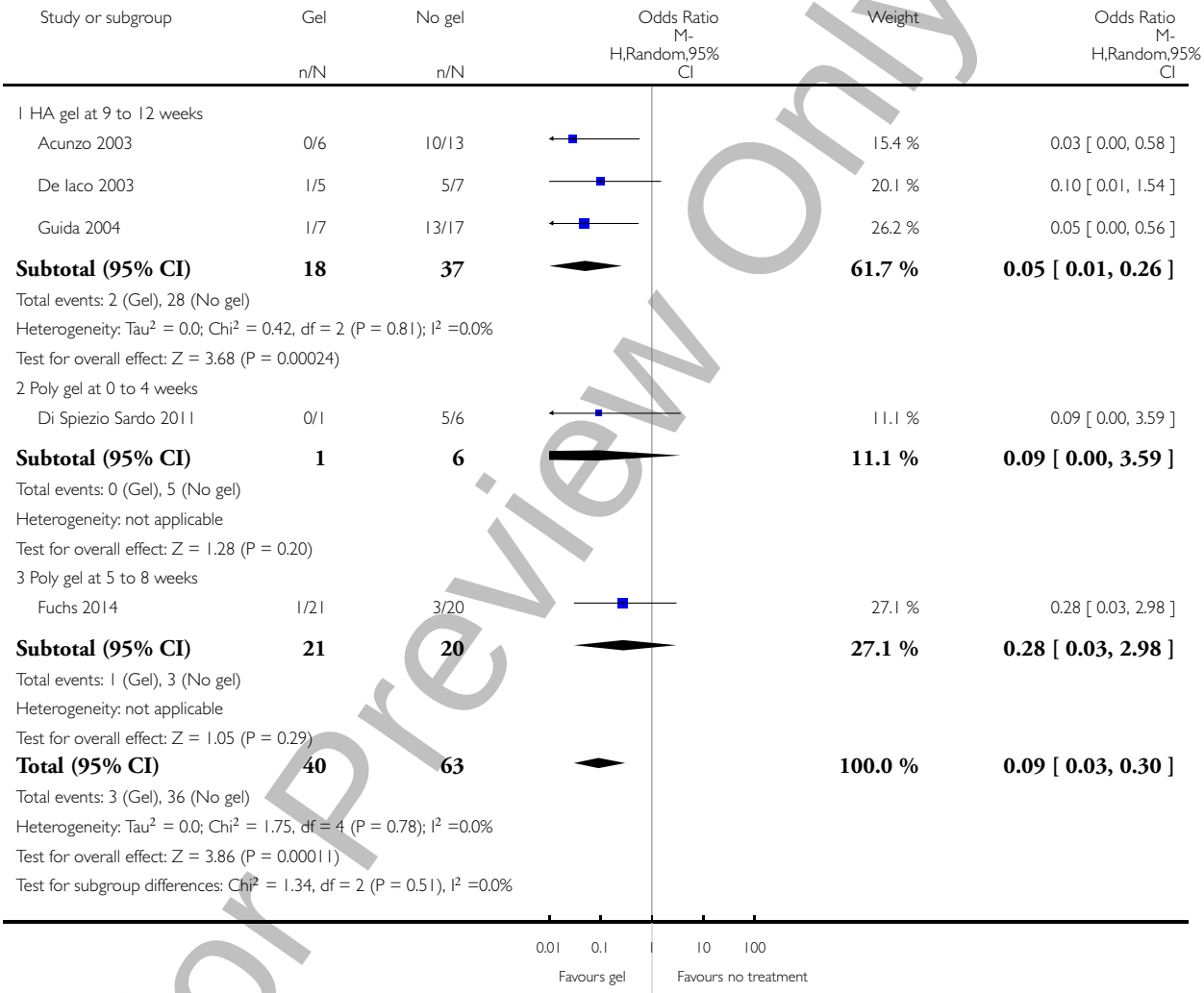


Analysis 4.5. Comparison 4 Gel vs no treatment, Outcome 5 Moderate or severe adhesions at second-look hysteroscopy.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 4 Gel vs no treatment

Outcome: 5 Moderate or severe adhesions at second-look hysteroscopy

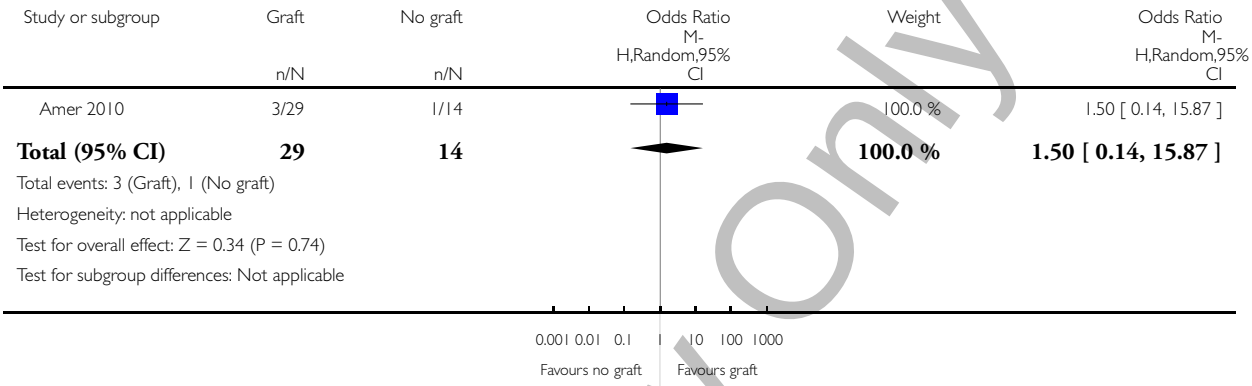


Analysis 6.1. Comparison 6 Graft vs no graft, Outcome 1 Live birth.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 6 Graft vs no graft

Outcome: 1 Live birth

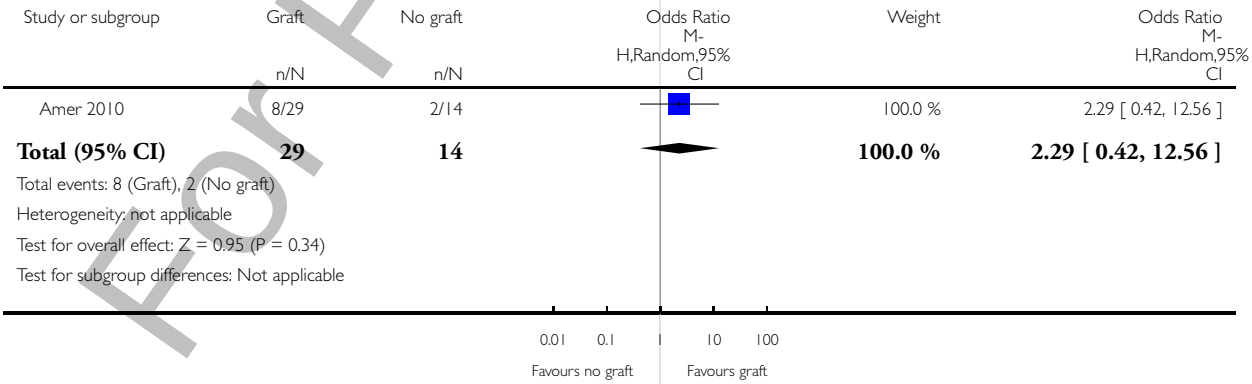


Analysis 6.2. Comparison 6 Graft vs no graft, Outcome 2 Clinical pregnancy.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 6 Graft vs no graft

Outcome: 2 Clinical pregnancy

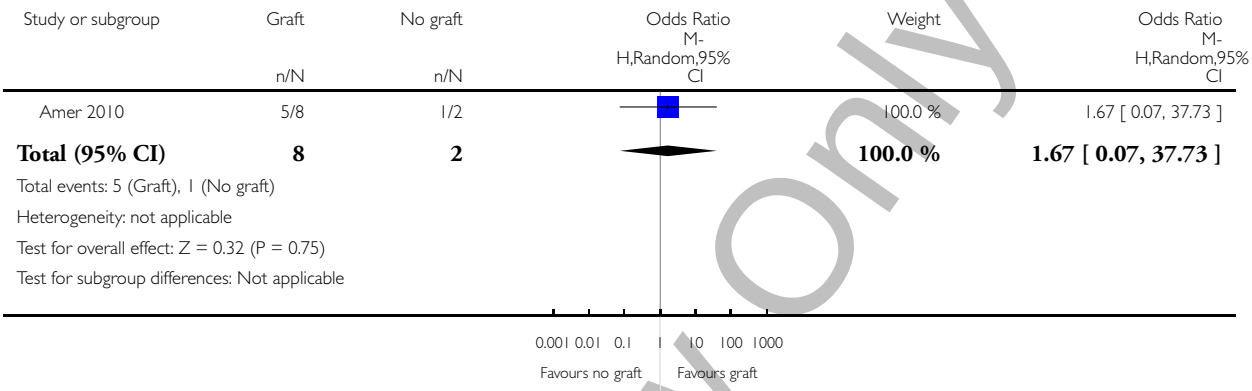


Analysis 6.3. Comparison 6 Graft vs no graft, Outcome 3 Miscarriage.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 6 Graft vs no graft

Outcome: 3 Miscarriage

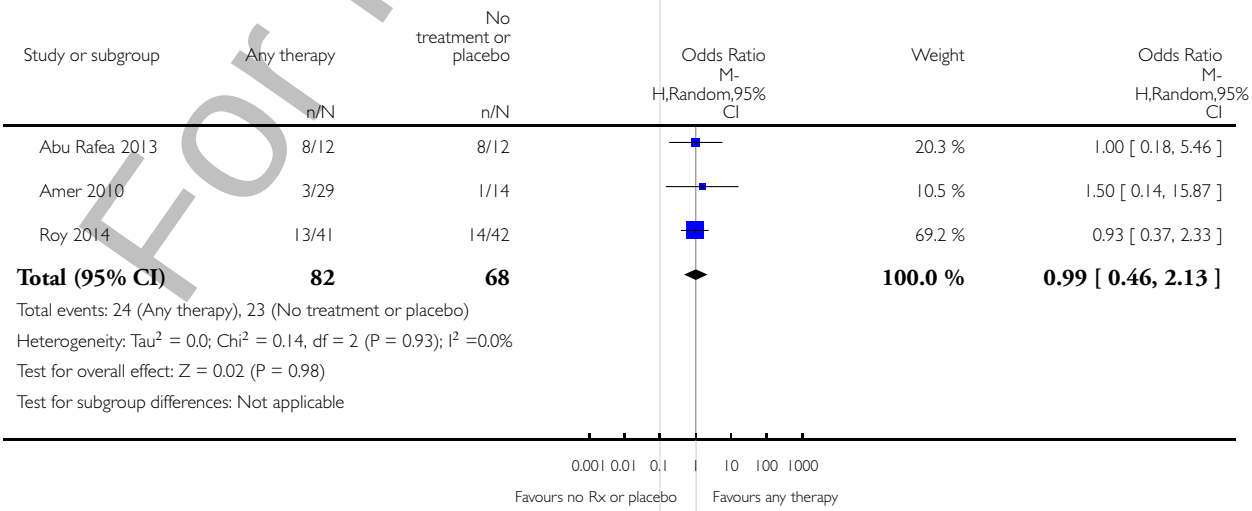


Analysis 7.1. Comparison 7 Any therapy vs no treatment or placebo, Outcome 1 Live birth.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 7 Any therapy vs no treatment or placebo

Outcome: 1 Live birth



Analysis 7.2. Comparison 7 Any therapy vs no treatment or placebo, Outcome 2 Clinical pregnancy.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 7 Any therapy vs no treatment or placebo

Outcome: 2 Clinical pregnancy

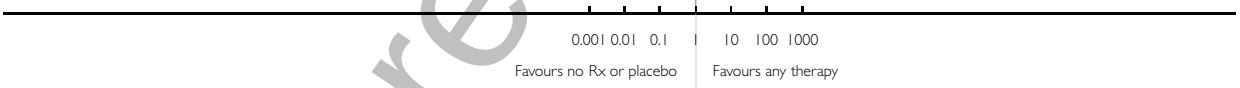
Study or subgroup	Any therapy n/N	No treatment or placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Abu Rafea 2013	11/12	11/12		5.5 %	1.00 [0.06, 18.08]
Amer 2010	8/29	2/14		15.9 %	2.29 [0.42, 12.56]
Fuchs 2014	7/21	3/20		19.8 %	2.83 [0.62, 13.04]
Roy 2014	15/41	17/42		58.8 %	0.85 [0.35, 2.06]
Total (95% CI)	**103**	**88**		**100.0 %**	**1.27 [0.65, 2.51]**

Total events: 41 (Any therapy), 33 (No treatment or placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 2.35$, df = 3 (P = 0.50); $I^2 = 0.0\%$

Test for overall effect: Z = 0.69 (P = 0.49)

Test for subgroup differences: Not applicable

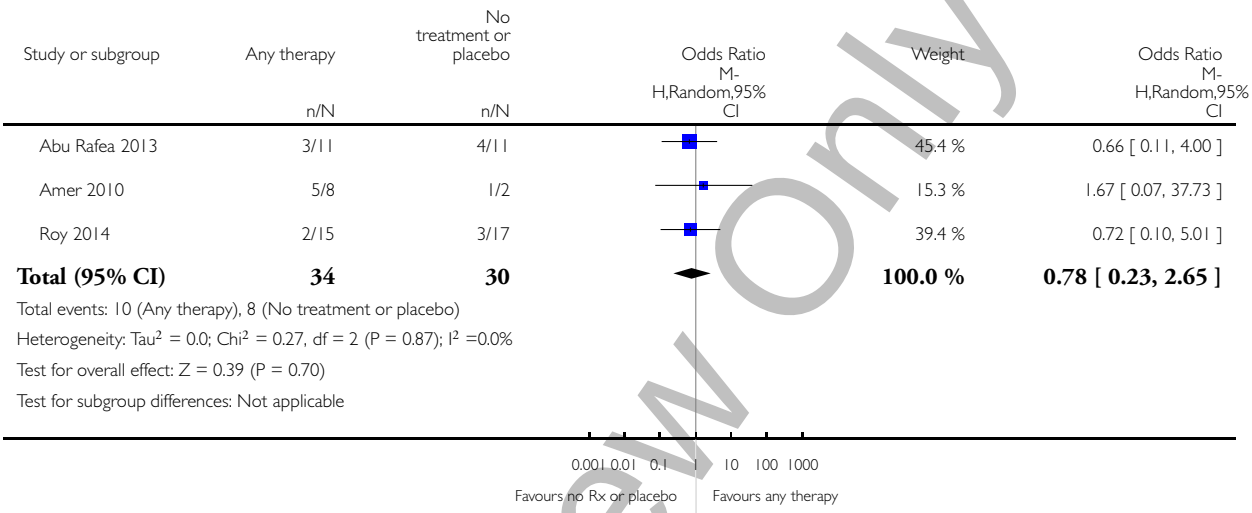


Analysis 7.3. Comparison 7 Any therapy vs no treatment or placebo, Outcome 3 Miscarriage.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 7 Any therapy vs no treatment or placebo

Outcome: 3 Miscarriage

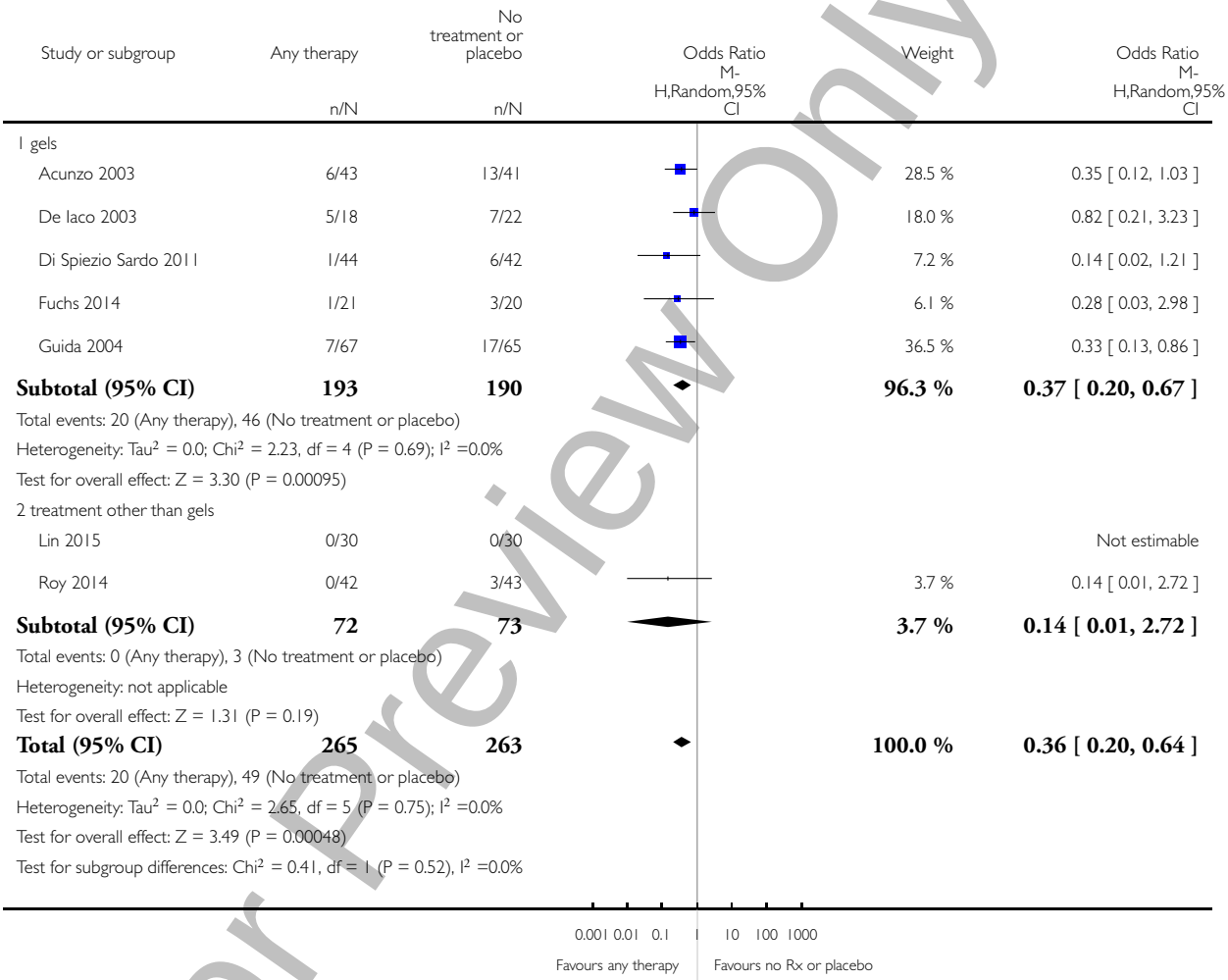


Analysis 7.4. Comparison 7 Any therapy vs no treatment or placebo, Outcome 4 Presence of intrauterine adhesions at second-look hysteroscopy.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 7 Any therapy vs no treatment or placebo

Outcome: 4 Presence of intrauterine adhesions at second-look hysteroscopy



Analysis 7.5. Comparison 7 Any therapy vs no treatment or placebo, Outcome 5 Mean adhesion scores.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 7 Any therapy vs no treatment or placebo

Outcome: 5 Mean adhesion scores

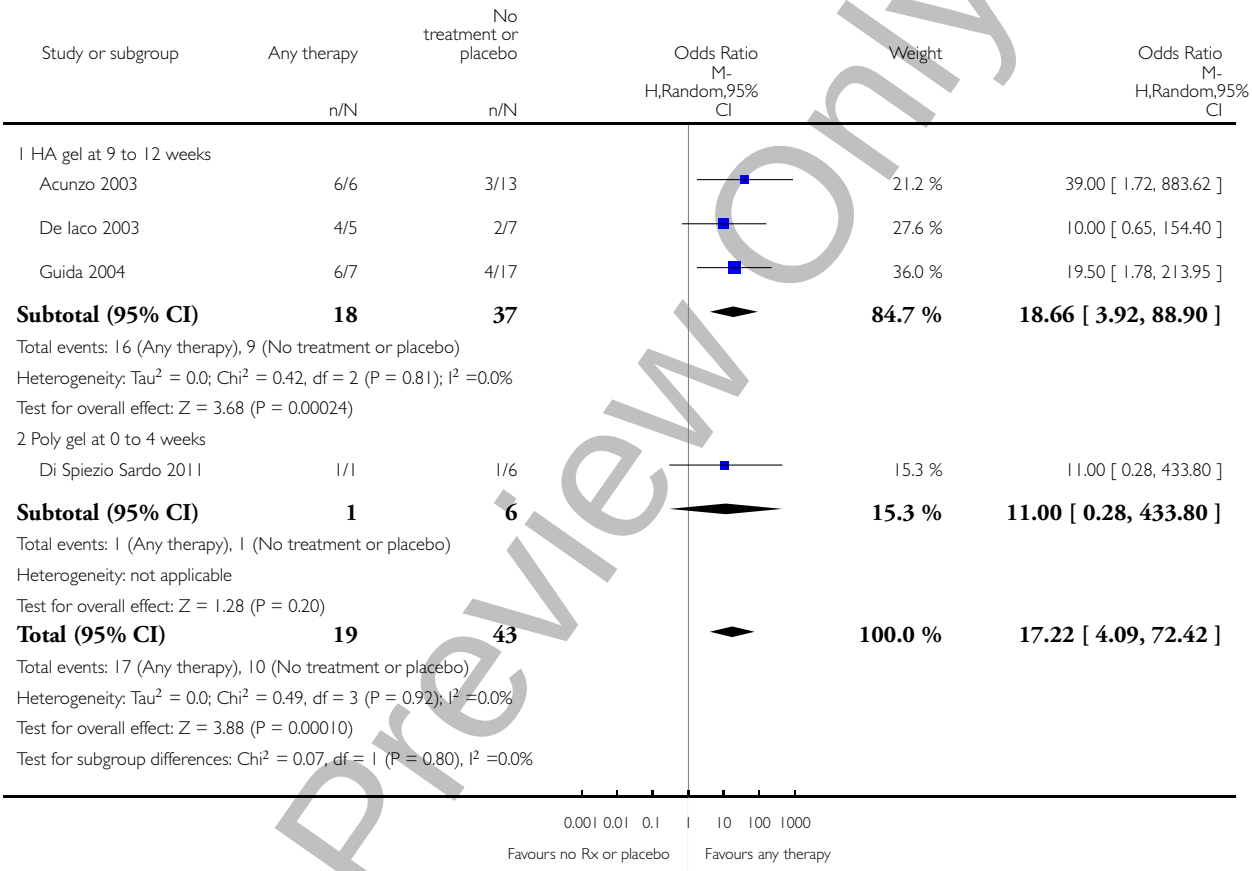
Study or subgroup	Any therapy N	Mean(SD)	No treatment or placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 in women treated for fibroids							
Guida 2004	4	2.25 (0.5)	8	3.5 (1.19)		24.1 %	-1.25 [-2.21, -0.29]
Subtotal (95% CI)	**4**		**8**			**24.1 %**	**-1.25 [-2.21, -0.29]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.55 (P = 0.011)							
2 in women treated for polyps							
Guida 2004	2	2 (0.1)	6	3.5 (0.54)		26.7 %	-1.50 [-1.95, -1.05]
Subtotal (95% CI)	**2**		**6**			**26.7 %**	**-1.50 [-1.95, -1.05]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.48 (P < 0.00001)							
3 in women treated for uterine septa							
Guida 2004	1	4 (0.1)	3	5.33 (1.15)		21.6 %	-1.33 [-2.65, -0.01]
Subtotal (95% CI)	**1**		**3**			**21.6 %**	**-1.33 [-2.65, -0.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.98 (P = 0.048)							
4 in women treated for intrauterine adhesions							
Acunzo 2003	6	2 (0.1)	13	5.3 (0.2)		27.6 %	-3.30 [-3.43, -3.17]
Subtotal (95% CI)	**6**		**13**			**27.6 %**	**-3.30 [-3.43, -3.17]**
Heterogeneity: not applicable							
Test for overall effect: Z = 47.91 (P < 0.00001)							
Total (95% CI)	**13**		**30**			**100.0 %**	**-1.90 [-3.21, -0.59]**
Heterogeneity: Tau² = 1.62; Chi² = 77.43, df = 3 (P<0.00001); I² =96%							
Test for overall effect: Z = 2.84 (P = 0.0046)							
Test for subgroup differences: Chi² = 77.43, df = 3 (P = 0.00), I² =96%							

Analysis 7.6. Comparison 7 Any therapy vs no treatment or placebo, Outcome 6 Mild adhesions at second-look hysteroscopy.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 7 Any therapy vs no treatment or placebo

Outcome: 6 Mild adhesions at second-look hysteroscopy

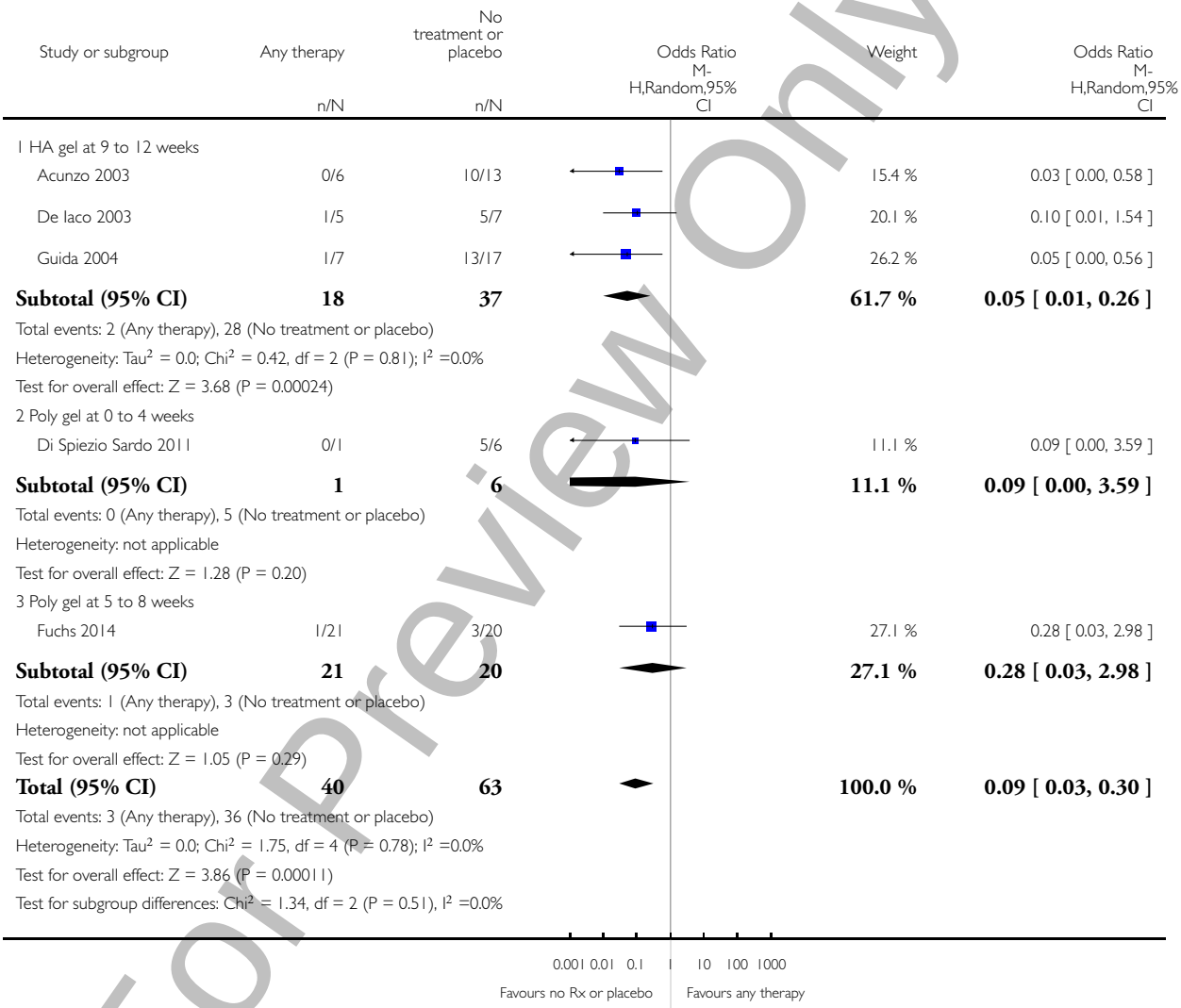


Analysis 7.7. Comparison 7 Any therapy vs no treatment or placebo, Outcome 7 Moderate or severe adhesions at second-look hysteroscopy.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 7 Any therapy vs no treatment or placebo

Outcome: 7 Moderate or severe adhesions at second-look hysteroscopy

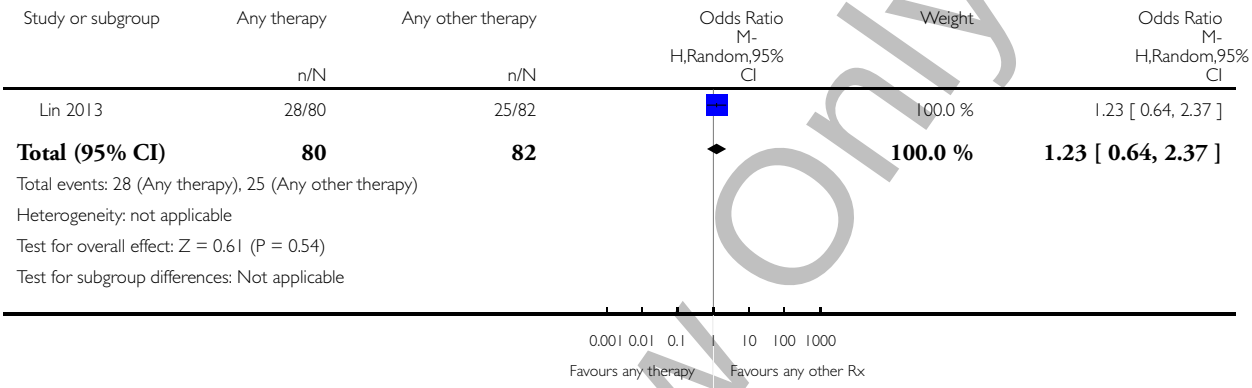


Analysis 8.1. Comparison 8 Any therapy vs any other therapy, Outcome 1 Presence of intrauterine adhesions at second-look hysteroscopy.

Review: Anti-adhesion therapy following operative hysteroscopy for treatment of female subfertility

Comparison: 8 Any therapy vs any other therapy

Outcome: 1 Presence of intrauterine adhesions at second-look hysteroscopy



APPENDICES

Appendix 1. 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"
25 records
Database: MDSG Specialised Register
Most recent update: 1 March 2015

Appendix 2. CENTRAL search strategy (CDSR)

#1MeSH descriptor: [Hysteroscopy] explode all trees(331)
#2hysteroscopic surgery (218)
#3operative hysteroscopy (153)
#4synechiolysis (6)
#5#1 or #2 or #3 or #4 (486)
#6barrier agent (478)
#7hyaluronic acid gel (151)
#8intrauterine balloon (76)
#9amnion graft (34)
#10estrogen treatment (4944)
#11MeSH descriptor: [Intrauterine Devices] explode all trees(528)
#12MeSH descriptor: [Anti-Bacterial Agents] explode all trees(9351)
#13#6 or #7 or #7 or #8 or #9 or #10 or #11 or #12 (15453)
#14intrauterine adhesions (83)
#15adhesion score (379)
#16reproductive outcome (2949)
#17#14 or #15 or #16 (3335)
#18#5 and #13 and #17 (26)
Trials (10)
10 records
Database: Cochrane Database of Systematic Reviews : Issue 2 of 12, February 2015
Most recent update: 1 March 2015

Appendix 3. MEDLINE search strategy (PubMed)

(((((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "drug therapy"[Subheading] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])))) AND ((((reproductive outcome) OR adhesion score) OR intrauterine adhesions) OR "Gynatresia"[Majr])) AND ((((((((("Anti-Bacterial Agents"[Majr]) OR "Intrauterine Devices"[Mesh]) OR oestrogen treatment) OR amnion graft) OR intrauterine balloon) OR gel) OR hyaluronan) OR hyaluronic acid gel) OR barrier agents) OR adhesion prevention)) AND (((((synechiolysis) OR operative hysteroscopy) OR "Gynecologic Surgical Procedures"[Majr]) OR hysteroscopic surgery) OR "Hysteroscopy"[Majr])
73 records
Database: MEDLINE using PubMed
Most recent update: 1 March 2015

Appendix 4. EMBASE search strategy (Embase.com)

#1'hysteroscopy'/exp OR 'hysteroscopy'(9,025)
#2hysteroscopic AND 'surgery' (2,789)
#3gynaecological AND 'surgery' (12,096)
#4operative AND 'hysteroscopy'(1,432)
#5synechiolysis (68)
#6#1 OR #2 OR #3 OR #4 OR #5 (20,934)
#7'adhesion'/exp AND 'prevention' (2,148)
#8barrier AND agents (9,304)
#9hyaluronic AND 'acid'/exp AND 'gel'/exp (17)
#10'hyaluronan'/exp (27,877)
#11'gel'/exp (44,845)
#12'intrauterine'/exp AND 'balloon'/exp (4)
#13'amnion'/exp AND graft (586)

#14'estrogen'/exp AND treatment (71,879)
#15'intrauterine'/exp AND 'device'/exp (53)
#16'antibiotics'/exp (1,028,785)
#17#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 (1,173,450)
#18'intrauterine'/exp AND 'adhesions'/exp (4)
#19'adhesion'/exp AND score (723)
#20reproductive AND outcome (35,161)
#21#18 OR #19 OR #20 (35,871)
#22#6 AND #17 AND #21 (123)
#23'clinical trial'/exp (1,003,328)
#24'randomized controlled trial'/exp (359,452)
#25'randomization'/exp (64,752)
#26'single blind procedure'/exp (19,275)
#27'double blind procedure'/exp (119,423)
#28'crossover procedure'/exp (41,489)
#29'placebo'/exp (265,749)
#30randomi?ed AND controlled AND trial* AND [embase]/lim (413,589)
#31rct AND [embase]/lim (16,308)
#32'random allocation'/exp AND [embase]/lim (40,184)
#33'randomly allocated' AND [embase]/lim (18,799)
#34'allocated randomly' AND [embase]/lim (1,753)
#35allocated NEAR/2 random AND [embase]/lim (714)
#36'single blind$' AND [embase]/lim (21,581)
#37'double blind$' AND [embase]/lim (168,521)
#38(treble OR triple) NEAR/2 blind$ AND [embase]/lim (379)
#39placebo$ AND [embase]/lim (318,688)
#40'prospective study'/exp (273,441)
#41#23 OR #24 OR 25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 (1,523,172)
#42'case study'/exp (32,238)
#43'case report'/exp AND [embase]/lim (1,443,120)
#44'abstract report'/exp (89,644)
#45'letter'/exp (839,411)
#46#42 OR #43 OR #44 OR #45 (2,271,738)
#47#41 NOT #46 (1,470,705)
#48'animal'/exp (19,993,393)
#49'human'/exp (15,560,245)
#50#48 NOT #49 (4,433,148)
#51#47 NOT #50 (1,416,737)
#52#22 AND #51 (32)
32 records
Database: EMBASE using Embase.com
Most recent update: 1 March 2015

Appendix 5. Web of Science search strategy (WoS Core Collection, BIOSIS PREVIEWS and BIOSIS CITATION INDEX)

WoS CORE COLLECTION:
1TS = (hysteroscopy) (3,618)
2TS = (hysteroscopic surgery) (677)
3TS = (operative hysteroscopy) (768)
4TS = (synechiolysis) (39)
5#1 OR #2 OR #3 OR #4 (3,948)
6TS = (barrier agent)(13,035)
7TS =(hyaluronic acid gel)(1,759)
8TS = (intrauterine balloon)(300)
9TS = (amnion graft)(132)
10TS = (estrogen treatment) (40,294)
11TS = (intrauterine device) (4,882)
12TS = (antibiotics) (227,315)
13#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 (286,701)
14TS =(intrauterine adhesions) (643)
15TS =(adhesion score) (3,711)
16TS = (reproductive outcome)(19,235)
17#14 OR #15 OR #16 (23,430)
18#5 AND #13 AND #17 (75)
19 TS =(randomized controlled trial) (266,295)
20 #18 AND #19 (7)
WoS BIOSIS PREVIEWS
1 TS =(hysteroscopy) (1,482)
2 TS =(hysteroscopic surgery) (535)
3 TS =(operative hysteroscopy) (263)
4 TS =(synechiolysis) (13)
5 #1 OR #2 OR #3 OR #4 (1,807)
6 TS =(barrier agent) (13,010)
7 TS =(hyaluronic acid gel) (664)
8 TS =(intrauterine balloon) (106)
9 TS =(amnion graft) (89)
10 TS =(estrogen treatment) (27,482)
11 TS =(intrauterine device) (2,193)
12 TS =(antibiotics) (149,479)
13 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 (191,994)
14 TS =(intrauterine adhesions) (294)
15 TS =(adhesion score) (2,293)
16 TS =(reproductive outcome) (83,068)
17 #14 OR #15 OR #16 (85,457)
18 #5 AND #13 AND #17 (42)
19 TS =(randomized controlled trial) (85,853)
20 #18 AND #19 (3)
WoS BIOSIS CITATION INDEX
1 TS =(hysteroscopy) (1,482)
2 TS =(hysteroscopic surgery) (535)
3 TS =(operative hysteroscopy) (263)
4 TS =(synechiolysis) (13)
5 #1 OR #2 OR #3 OR #4 (1,807)
6 TS =(barrier agent) (13,010)
7 TS =(hyaluronic acid gel) (664)

8 TS =(intrauterine balloon) (106)
9 TS =(amnion graft) (89)
10 TS =(estrogen treatment) (27,484)
11 TS =(intrauterine device) (2,193)
12 TS =(antibiotics) (149,482)
13 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 (191,999)
14 TS =(intrauterine adhesions) (294)
15 TS =(adhesion score) (2,294)
16 TS =(reproductive outcome) (83,079)
17 #14 OR #15 OR #16 (85,469)
18 #5 AND #13 AND #17 (42)
19 TS =(randomized controlled trial) (85,914)
20 #18 AND #19 (3)
13 records
Database: Web of Science (WoS)
Most recent update: 1 March 2015

Appendix 6. CINAHL search strategy (EBSCOHOST)

S1 TX hysteroscopy (402)
S2 TX hysteroscopic surgery (22)
S3 TX operative hysteroscopy (21)
S4 TX synechiolysis (1)
S5 S1 OR S2 OR S3 OR S4 (407)
S6 “”barrier agent“” (20,804)
S7 TX hyaluronic acid gel (23)
S8 TX intrauterine balloon (19)
S9 TX amnion graft (3)
S10 TX estrogen treatment (324)
S11 TX intrauterine device (340)
S12 TX antibiotics (24,869)
S13 S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 (45,659)
S14 TX intrauterine adhesions (12)
S15 TX adhesion score (13)
S16 TX reproductive outcome (105)
S17 S14 OR S15 OR S16 (130)
S18 S5 AND S13 AND S17 (3)
S19 (MH “Clinical Trials”) (81,314)
S20 PT clinical trial* (51,840)
S21 (MH “Randomized Controlled Trials”) (21,688)
S22 PT randomized controlled trial* (26,173)
S23 (MH “Random Assignment”) (31,765)
S24 TX Randomi*ation (3,738)
S25 TX single blind* (7,444)
S26 TX double blind* (624,628)
S27 TX triple blind* (108)
S28 “”TX treble blind*“” (34,790)
S29 TX Placebo* (26,693)
S30 TX prospective stud* (179,626)
S31 S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 (863,237)
S32 S18 AND S31 (2)
2 records

Database: CINAHL using EBSCOHOST
Most recent update: 1 March 2015

Appendix 7. Items of the pilot-tested data extraction form

1. Source

- study ID
- report ID
- review 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 inclusion 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 randomly assigned
- number of women excluded
- number of women withdrawn and lost to follow-up
- number of women analysed

Study setting

- single- or multi-centre
- 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 study participants

Baseline characteristics

- age
- primary or secondary subfertility
- duration of subfertility
- diagnostic workup: 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 hysteroscopic procedure
- detailed description of anti-adhesion therapy

5. Interventions

Total number of intervention groups

Absence of other interventions in treatment and control groups

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
- presence of intrauterine adhesions at second-look hysteroscopy

Secondary outcomes

- 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 × 2 table
- estimate of effect with 95% CI
- subgroup analyses

7. Miscellaneous

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

CONTRIBUTIONS OF AUTHORS

JB coordinated writing of this review.

JK co-authored the protocol for the Background section, assisted in the search for and selection of studies and was involved in data extraction and risk of bias assessment.

SW, FB and TD co-authored the protocol, provided comments and criticisms on the methods and content of the review and were involved in data extraction and risk of bias assessment.

BWM was responsible for overall supervision of the methods of this review and was consulted 'ad hoc' for assistance in resolving disagreements.

DECLARATIONS OF INTEREST

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

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 supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- In the protocol, we defined two primary outcomes: live birth (positive outcome) and presence of IUAs at second-look hysteroscopy (adverse outcome). We defined as secondary outcomes the following: clinical pregnancy, miscarriage, mean adhesion scores and severity of adhesions at second-look hysteroscopy. In the full review, we decided to include only one primary outcome, namely, live birth or ongoing pregnancy - the primary outcome of interest for women suffering from subfertility. Clinical pregnancy, miscarriage, presence of IUAs at second-look hysteroscopy, mean adhesion scores and severity of adhesions present at second-look hysteroscopy were defined as secondary outcomes. We made this change on the basis of advice provided by the peer review editorial team in the interest of simplification and readability. We similarly avoided use of the outcome 'incidence of de novo adhesions'; several included studies enrolled participants with existing IUAs, and at second-look hysteroscopy the distinction between de novo and recurrent adhesions may not be possible and may not be clinically relevant.

- Term delivery was used in the review as a surrogate outcome for live birth because the number of studies reporting live birth or ongoing pregnancy was very limited.

- The protocol prespecified that data would be extracted simultaneously and independently by two review authors. For practical reasons, data were extracted by at least one pair of review authors: JB extracted data from all studies, and TD/FB/JK/SW divided all studies between them, and each extracted data from only a portion of the included studies. In cases of disagreement, BWM acted as a 'third' review author for arbitration. See Potential biases in the review process.

- We clarified the inclusion criteria to specify that studies in which at least a proportion of women were undergoing operative hysteroscopy for subfertility were eligible.