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Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities (Review)

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[Intervention Review]

Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities

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ABSTRACT

Background

Observational studies suggest higher pregnancy rates after the hysteroscopic removal of endometrial polyps, submucous fibroids, uterine septum or intrauterine adhesions, which are present in 10% to 15% of women seeking treatment for subfertility.

Objectives

To assess the effects of the hysteroscopic removal of endometrial polyps, submucous fibroids, uterine septum or intrauterine adhesions suspected on ultrasound, hysterosalpingography, diagnostic hysteroscopy or any combination of these methods in women with otherwise unexplained subfertility or prior to intrauterine insemination (IUI), in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI).

Search methods

We searched the following databases from their inception to 16 April 2018; The Cochrane Gynaecology and Fertility Group Specialised Register, the Cochrane Central Register of Studies Online, ; MEDLINE, Embase, CINAHL, and other electronic sources of trials including trial registers, sources of unpublished literature, and reference lists. We handsearched the American Society for Reproductive Medicine (ASRM) conference abstracts and proceedings (from 1 January 2014 to 12 May 2018) and we contacted experts in the field.

Selection criteria

Randomised comparison between operative hysteroscopy versus control for unexplained subfertility associated with suspected major uterine cavity abnormalities.

Randomised comparison between operative hysteroscopy versus control for suspected major uterine cavity abnormalities prior to medically assisted reproduction.

Primary outcomes were live birth and hysteroscopy complications. Secondary outcomes were pregnancy and miscarriage.

Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities (Review)

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Data collection and analysis

Two review authors independently assessed studies for inclusion and risk of bias, and extracted data. We contacted study authors for additional information.

Main results

Two studies met the inclusion criteria.

1. Randomised comparison between operative hysteroscopy versus control for unexplained subfertility associated with suspected major uterine cavity abnormalities.

In women with otherwise unexplained subfertility and submucous fibroids, we were uncertain whether hysteroscopic myomectomy improved the clinical pregnancy rate compared to expectant management (odds ratio (OR) 2.44, 95% confidence interval (CI) 0.97 to 6.17; $P = 0.06$, 94 women; very low-quality evidence). We are uncertain whether hysteroscopic myomectomy improves the miscarriage rate compared to expectant management (OR 1.54, 95% CI 0.47 to 5.00; $P = 0.47$, 94 women; very low-quality evidence). We found no data on live birth or hysteroscopy complication rates. We found no studies in women with endometrial polyps, intrauterine adhesions or uterine septum for this randomised comparison.

2. Randomised comparison between operative hysteroscopy versus control for suspected major uterine cavity abnormalities prior to medically assisted reproduction.

The hysteroscopic removal of polyps prior to IUI may have improved the clinical pregnancy rate compared to diagnostic hysteroscopy only: if 28% of women achieved a clinical pregnancy without polyp removal, the evidence suggested that 63% of women (95% CI 45% to 89%) achieved a clinical pregnancy after the hysteroscopic removal of the endometrial polyps (OR 4.41, 95% CI 2.45 to 7.96; $P < 0.00001$, 204 women; low-quality evidence). We found no data on live birth, hysteroscopy complication or miscarriage rates in women with endometrial polyps prior to IUI. We found no studies in women with submucous fibroids, intrauterine adhesions or uterine septum prior to IUI or in women with all types of suspected uterine cavity abnormalities prior to IVF/ICSI.

Authors' conclusions

Uncertainty remains concerning an important benefit with the hysteroscopic removal of submucous fibroids for improving the clinical pregnancy rates in women with otherwise unexplained subfertility. The available low-quality evidence suggests that the hysteroscopic removal of endometrial polyps suspected on ultrasound in women prior to IUI may improve the clinical pregnancy rate compared to simple diagnostic hysteroscopy. More research is needed to measure the effectiveness of the hysteroscopic treatment of suspected major uterine cavity abnormalities in women with unexplained subfertility or prior to IUI, IVF or ICSI.

PLAIN LANGUAGE SUMMARY

Hysteroscopy for treating suspected abnormalities of the cavity of the womb in women having difficulty becoming pregnant

Review question

Cochrane authors reviewed the evidence about the effect of the hysteroscopic treatment of suspected abnormalities of the cavity of the womb in women having difficulty becoming pregnant.

Background

Human life starts when a fertilised egg has successfully implanted in the inner layer of the cavity of the womb. It is believed that abnormalities originating from this site, such as polyps (abnormal growth of tissue), fibroids (non-cancerous growth), septa (upside-down, triangular-shaped piece of tissue which divides the womb) or adhesions (scar tissue that sticks the walls of the womb together), may disturb this event. The removal of these abnormalities by doing a hysteroscopy using a very small diameter inspecting device might therefore increase the chance of becoming pregnant either spontaneously or after specialised fertility treatment, such as insemination or in vitro fertilisation.

Study characteristics

We found two studies. The first study compared the removal of fibroids versus no removal in 94 women wishing to become pregnant spontaneously from January 1998 to April 2005. The second study compared the removal of polyps versus simple hysteroscopy only in

204 women before insemination with husband's sperm from January 2000 to February 2004. The evidence is current to April 2018. Neither study reported funding sources.

Key results

In women with fibroids wishing to become pregnant spontaneously we were uncertain whether removal of the fibroids improved the pregnancy or miscarriage rate compared to usual management: uncertainty remains because the number of women (94) and the number of pregnancies (30) were too small and the quality of the evidence was very low. We found no data on live birth or complications due to surgery. We found no studies on women with polyps, septa or adhesions.

The hysteroscopic removal of polyps prior to intrauterine insemination (IUI; a fertility treatment where sperm is placed inside a woman's womb to fertilise the egg) is may improve the pregnancy rate compared to not removing polyps. If 28% of women become pregnant without surgery, the evidence suggests that about 63% of women will become pregnant following removal of polyps. We found no data on number of live births, hysteroscopy complications or miscarriage rates prior to IUI. We retrieved no studies in women before other fertility treatments.

More studies are needed before hysteroscopy can be proposed as a fertility-enhancing procedure in the general population of women having difficulty becoming pregnant.

Quality of the evidence

The quality of the evidence retrieved was very low to low due to the limited number of participants and the poor design of the studies.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Operative hysteroscopy versus control in women with otherwise unexplained subfertility and suspected major uterine cavity abnormalities						
Patient or population: women with submucous fibroids and otherwise unexplained subfertility Settings: infertility centre in Rome, Italy Intervention: hysteroscopic removal of 1 submucous fibroid \leq 40 mm Comparison: no surgery						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No surgery	Myomectomy				
Live birth	No data reported.					
Adverse events: hysteroscopy complications	No data reported.					
Clinical pregnancy ^d Ultrasound 12 months	214 per 1000	400 per 1000 (209 to 627)	OR 2.44 (0.97 to 6.17)	94 (1 study)	⊕○○○ Very low ^{b,c}	-
Adverse events: miscarriage ^d Ultrasound 12 months	119 per 1000	172 per 1000 (63 to 477)	OR 1.54 (0.47 to 5.00)	94 women (1 study)	⊕○○○ Very low ^{b,c}	-

*The basis for the **assumed risk** is the control group risk of the single included study (Casini 2006). 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.

^aClinical pregnancy defined by the visualisation of an embryo with cardiac activity at six to seven weeks' gestational age.

^bDowngraded by two levels for very serious risk of bias (unclear allocation concealment, high risk of selective outcome reporting and unclear whether there is other bias caused by imbalance in the baseline characteristics).

^cDowngraded by one level for serious imprecision (wide confidence interval of the effect size estimate).

^dMiscarriage was defined by the clinical loss of an intrauterine pregnancy between the 7th and 12th weeks of gestation.

BACKGROUND

Description of the condition

Subfertility is “a disease of the reproductive system defined by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual intercourse” according to the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of assisted reproductive technology (Zegers-Hochschild 2017) (see: www.icmartivf.org/ivf-glossary.html). It is estimated that 72.4 million women are subfertile and that 40.5 million of these women are currently seeking fertility treatment (Boivin 2007). Unexplained subfertility usually refers to a diagnosis (or lack of diagnosis) made in couples in whom all the standard investigations such as tests of ovulation, tubal patency and semen analysis are normal: it can be found in as many as 30% to 40% of subfertile couples (Ray 2012).

The evaluation of the uterine cavity seems a basic step in the investigation of all subfertile women since the uterine cavity and its inner layer, the endometrium, are assumed to be important for the implantation of the human embryo, called a blastocyst. Nevertheless, the complex mechanisms leading to successful implantation are still poorly understood (Taylor 2008). Despite the huge investment in research and developments of the technologies and biology involved in medically assisted reproduction (MAR), the maximum implantation rate per embryo transferred still remains only 30% (Andersen 2008). The different phases of the implantation process are established by the complex interchange between the blastocyst and the endometrium (Singh 2011).

Major uterine cavity abnormalities can be found in 10% to 15% of women seeking treatment for subfertility; they usually consist of the presence of excessive normal uterine tissue (Wallach 1972). The most common acquired uterine cavity abnormality is an endometrial polyp. This benign, endometrial stalk-like mass protrudes into the uterine cavity and has its own vascular supply. Depending on the population under study and the applied diagnostic test, endometrial polyps can be found in 1% to 41% of the subfertile population (Silberstein 2006). A fibroid is an excessive growth originating from the muscular part of the uterine cavity. Fibroids are present in 2.4% of subfertile women without any other obvious cause of subfertility (Donnez 2002). A submucous fibroid is located underneath the endometrium and is thought to interfere with fertility by deforming the uterine cavity. Intrauterine adhesions are fibrous tissue strings connecting parts of the uterine wall. They are commonly caused by inflammation or iatrogenic tissue damage (meaning involuntarily caused by a physician's intervention, for example an aspiration curettage after miscarriage) and are present in 0.3% to 14% of subfertile women (Fatemi 2010).

A septate uterus is a congenital malformation in which the longitudinal band separating the left and right Müllerian ducts, which form the uterus in the human female fetus, has not been entirely

resorbed. A uterine septum is present in 1% to 3.6% of women with otherwise unexplained subfertility (Sarvelos 2008).

Ultrasonography (US), preferably transvaginally (TVS), is used to screen for possible endometrium or uterine cavity abnormalities in the work-up of subfertile women. This evaluation can be expanded with hysterosalpingography (HSG), saline infusion/gel instillation sonography (SIS/GIS) and diagnostic hysteroscopy. Diagnostic hysteroscopy is generally considered as the gold standard procedure for the assessment of the uterine cavity since it enables direct visualisation; moreover, treatment of intrauterine pathology can be done in the same setting (Bettocchi 2004). Nevertheless, even for experienced gynaecologists, the hysteroscopic diagnosis of the major uterine cavity abnormalities may be problematic (Kasius 2011a).

Description of the intervention

Hysteroscopy is performed for the evaluation, or for the treatment of the uterine cavity, tubal ostia and endocervical canal in women with uterine bleeding disorders, Müllerian tract anomalies, retained intrauterine contraceptives or other foreign bodies, retained products of conception, desire for sterilisation, recurrent miscarriage and subfertility. If the procedure is intended for evaluating the uterine cavity only, it is called a diagnostic hysteroscopy. If the observed pathology requires further treatment, the procedure is called an operative hysteroscopy. In everyday practice, a diagnostic hysteroscopy confirming the presence of pathology will be followed by an operative hysteroscopy in a symptomatic woman. Hysteroscopy allows the 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° to allow direct viewing or offset at various angles to provide a fore-oblique view. Advances in fiberoptic technology have led to the miniaturisation of the telescopes without compromising the image quality. The total working diameters of modern diagnostic hysteroscopes are typically 2.5 mm to 4.0 mm. Operative hysteroscopy requires adequate visualisation through a continuous fluid circulation using an inflow and an outflow channel. The outer diameters of modern operative hysteroscopes have been reduced to a diameter between 4.0 mm and 5.5 mm. The sheath system contains one or two 1.6 mm to 2.0 mm working channels for the insertion of 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.

Most diagnostic and many operative procedures can be done in a clinic setting using local anaesthesia and fluid distension media, while more complex procedures are generally performed as day surgery under general anaesthesia (Clark 2005). Operative hysteroscopic procedures require a complex instrumentation setup,

special training of the surgeon, and appropriate knowledge and management of complications (Campo 1999).

Although complications from hysteroscopy are rare, they can be potentially life threatening. One multicentre study including 13,600 diagnostic and operative hysteroscopic procedures performed in 82 centres reported a complication rate of 0.28%. Diagnostic hysteroscopy had a significantly lower complication rate compared to operative hysteroscopy (0.13% with diagnostic versus 0.95% with operative). The most common complication of both types of hysteroscopy was uterine perforation (0.13% with diagnostic versus 0.76% with operative). Fluid intravasation occurred almost exclusively in operative procedures (0.02%). Intrauterine adhesiolysis was associated with the highest incidence of complications (4.5%); all of the other procedures had complication rates of less than 1% (Jansen 2000).

How the intervention might work

It is assumed that major uterine cavity abnormalities may interfere with factors that regulate the blastocyst-endometrium interplay, for example hormones and cytokines, precluding the possibility of pregnancy. Many hypotheses have been formulated in the literature of how endometrial polyps (Shokeir 2004; Silberstein 2006; Taylor 2008; Yanaihara 2008), submucous fibroids (Pritts 2001; Somigliana 2007; Taylor 2008), intrauterine adhesions (Yu 2008), and uterine septum (Fedele 1996) are likely to disturb the implantation of the human embryo; nevertheless, the precise mechanisms of action through which each one of these major uterine cavity abnormalities affects this essential reproductive process are poorly understood. The foetal-maternal conflict hypothesis tries to explain how a successful pregnancy may establish itself despite the intrinsic genomic instability of human embryos through the specialist functions of the endometrium, in particular its capacity for cyclic spontaneous decidualisation, shedding and regeneration. An excellent indepth review linking basic research of human implantation with clinical practice can be found elsewhere (Lucas 2013).

For endometrial polyps, submucous fibroids, intrauterine adhesions and uterine septum, observational studies have shown a clear improvement in the spontaneous pregnancy rate after the hysteroscopic removal of the abnormality (Taylor 2008). Two observational studies suggested a better reproductive outcome following hysteroscopic polypectomy in women prior to intrauterine insemination (IUI) (Kalampokas 2012; Shohayeb 2011). The chance for pregnancy is significantly lower in subfertile women with submucous fibroids compared to other causes of subfertility according to one systematic review and meta-analysis of 11 observational studies (Pritts 2001; Pritts 2009). Three observational studies found a major benefit for removing a uterine septum by hysteroscopic metroplasty in subfertile women with a uterine septum (Mollo 2009; Shokeir 2011; Tomaz eviç 2010).

Why it is important to do this review

An updated National Institute for Health and Care Excellence (NICE) guideline on fertility assessment and treatment states that “ Women should not be offered hysteroscopy on its own as part of the initial investigation unless clinically indicated because the effectiveness of surgical treatment of uterine abnormalities on improving pregnancy rates has not been established ” (NICE 2013). However, there is a trend in reproductive medicine that is developing towards diagnosis and treatment of all major uterine cavity abnormalities prior to fertility treatment. This evolution can be explained by three reasons. First, diagnostic hysteroscopy is generally accepted in everyday clinical practice as the ‘gold standard’ for identifying uterine abnormalities because it allows direct visualisation of the uterine cavity (Golan 1996). Second, since 2004 several randomised controlled trials (RCTs) have demonstrated the technical feasibility and the high patient satisfaction rate in women undergoing both diagnostic and operative hysteroscopy for various reasons including subfertility (Campo 2005; De Placido 2007; Garbin 2006; Guida 2006; Kabli 2008; Marsh 2004; Sagiv 2006; Shankar 2004; Sharma 2005). Third, in a subfertile population screened systematically by diagnostic hysteroscopy, the incidence of newly detected intrauterine pathology may be as high as 50% (Campo 1999; De Placido 2007).

This review aimed to summarise and critically appraise the current evidence on the effectiveness of operative hysteroscopic interventions in subfertile women with major uterine cavity abnormalities, both in women with unexplained subfertility and women bound to undergo MAR. Since uterine cavity abnormalities may negatively affect the uterine environment, and therefore the likelihood of conceiving (Rogers 1986), it has been recommended that these abnormalities be diagnosed and treated by hysteroscopy to improve the cost-effectiveness in subfertile women undergoing MAR, where recurrent implantation failure is inevitably associated with a higher economic burden to society.

The study of the association between subfertility and major uterine cavity abnormalities might increase our current understanding of the complex mechanisms of human embryo implantation. This could lead to the development of cost-effective strategies in reproductive medicine with benefits for both the individual woman experiencing subfertility associated with major uterine cavity abnormalities as well as for society, in a broader perspective.

OBJECTIVES

To assess the effects of the hysteroscopic removal of endometrial polyps, submucous fibroids, uterine septum or intrauterine adhesions suspected on ultrasound, hysterosalpingography, diagnostic hysteroscopy or any combination of these methods in women with otherwise unexplained subfertility or prior to intrauterine insemination.

nation (IUI), in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI).

METHODS

Criteria for considering studies for this review

Types of studies

Inclusion criteria

- Trials that were either clearly randomised or claimed to be randomised and did not have evidence of inadequate sequence generation such as date of birth or hospital number were eligible for inclusion.
- Cluster trials were eligible if the individually randomised women were the unit of analysis.
- Cross-over trials were eligible for completeness but we planned to use only pre-cross-over data for meta-analysis.

Exclusion criteria

- Quasi-randomised trials.

Types of participants

Inclusion criteria

- Women of reproductive age with otherwise unexplained subfertility and endometrial polyps, submucous fibroids, septate uterus or intrauterine adhesions detected by US, SIS, GIS, HSG, diagnostic hysteroscopy or any combination of these methods. Besides unexplained subfertility as the main clinical problem, other gynaecological complaints, such as pain or bleeding, might or might not be present.
- Women of reproductive age with subfertility, undergoing IUI, IVF or ICSI with endometrial polyps, submucous fibroids, septate uterus or intrauterine adhesions detected by US, SIS, GIS, HSG, diagnostic hysteroscopy or any combination of these methods.

Exclusion criteria

- Women of reproductive age with no major uterine cavity abnormalities detected by US, SIS, GIS, HSG, diagnostic hysteroscopy or any combination of these methods.
- Women of reproductive age with subfertility and intrauterine cavity abnormalities other than endometrial polyps, submucous fibroids, intrauterine adhesions and septate uterus,

for example, subserous or intramural fibroids without cavity deformation on hysteroscopy, acute or chronic endometritis, adenomyosis or other so-called 'subtle focal' lesions.

- Women of reproductive age with endometrial polyps, submucous fibroids, intrauterine adhesions or septate uterus without subfertility.
- Women of reproductive age with recurrent pregnancy loss.

Types of interventions

We addressed two types of randomised interventions; within both comparisons we stratified the suspected major uterine cavity abnormalities into endometrial polyps, submucous fibroids, uterine septum and intrauterine adhesions. For the second comparison, there was a stratification into IUI, IVF or ICSI.

- Operative hysteroscopy versus control in women with otherwise unexplained subfertility and suspected major uterine cavity abnormalities diagnosed by US, SIS, GIS, HSG, diagnostic hysteroscopy or any combination of these methods.
- Operative hysteroscopy versus control in women undergoing IUI, IVF or ICSI with suspected major uterine cavity abnormalities diagnosed by US, SIS, GIS, HSG, diagnostic hysteroscopy or any combination of these methods.

Types of outcome measures

Primary outcomes

- Effectiveness: live birth, defined as a delivery of a live foetus after 20 completed weeks of gestational age that resulted in at least one live baby born. The delivery of a singleton, twin or multiple pregnancy was counted as one live birth.
- Adverse events: hysteroscopy complications, defined as any complication due to hysteroscopy.

Secondary outcomes

- Pregnancy
 - Ongoing pregnancy, defined as a pregnancy surpassing the first trimester or 12 weeks of pregnancy.
 - Clinical pregnancy with foetal heartbeat, defined as a pregnancy diagnosed by US or clinical documentation of at least one foetus with a heartbeat (Zegers-Hochschild 2017).
 - Clinical pregnancy, defined as a pregnancy diagnosed by US visualisation of one or more gestational sacs or definitive clinical signs of pregnancy (Zegers-Hochschild 2017).
- Adverse events: miscarriage, defined as the spontaneous loss of a clinical pregnancy before 20 completed weeks of gestation, or if gestational age was unknown a foetus with a weight of 400 g or less.

We planned to report the minimally important clinical difference (MICD) for the primary outcome of live birth. An MICD of 5%

for the live birth rate was predefined as being relevant for the benefits. The imputation of this value was based on data from a clinical decision analysis on screening hysteroscopy prior to IVF (Kasius 2011b).

Search methods for identification of studies

An updated search was done in liaison with the Cochrane Gynaecology and Fertility (CGF) Group Information Specialist (Marian Showell).

Two review authors (JB and SVW) independently performed a comprehensive search of all published and unpublished reports that described hysteroscopy in subfertile women with endometrial polyps, submucous fibroids, intrauterine adhesions or septate uterus, or undergoing MAR. The search strategy was not limited by language, year of publication or document format. We merged all the retrieved citations from the CGF Specialised Register, the Cochrane Central Register of Studies Online (CENTRAL), MEDLINE, Embase, Web of Science, the BIOSIS PREVIEWS and handsearch-related articles and removed duplicates using specialised software (EndNote Web 3.5; www.myendnoteweb.com/EndNoteWeb.html; last done: 12 May 2018).

Electronic searches

For the 2018 update of this Cochrane Review, we searched the following bibliographic databases, trial registers and websites:

The Cochrane Gynaecology and Fertility Group's (CGF) Specialised Register, searched on 16 April 2018, PROCITE platform (Appendix 1), CENTRAL Register of Studies Online (CRSO), searched on 16 April 2018, web platform (Appendix 2), MEDLINE OvidSP (searched from 1946 to 16 April 2018) (Appendix 3), and Embase OvidSP (searched from 1980 to 16 April 2018) (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 using the PubMed format which appears in the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 6.4.11.1, box 6.4.a) (Higgins 2011).

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

Other electronic sources of trials were:

- Database of Abstracts of Reviews of Effectiveness (DARE) and the Health Technology Assessment Database (HTA Database) through the Centre for Reviews and Dissemination (searched 12 May 2018) (www.crd.york.ac.uk);
- National Guideline Clearinghouse (www.guideline.gov) for evidence-based guidelines (searched 12 May 2018);
- BIOSIS previews through ISI Web of Knowledge (isiwebofknowledge.com) and CINAHL (www.cinahl.com)

through EBSCOhost available at the Biomedical Library Gasthuisberg of the Catholic University of Leuven (from 1961 to 1 May 2018) (Appendix 5);

- trial registers for ongoing and registered trials: Current Controlled Trials (www.controlled-trials.com), ClinicalTrials.gov provided by the US National Institutes of Health (clinicaltrials.gov/ct2/home) and the WHO International Clinical Trials Registry Platform search portal (apps.who.int/trialsearch/) (searched 12 May 2018);
- citation indexes: Science Citation Index through Web of Science (scientific.thomson.com/products/sci/) - SCI-EXPANDED (2014 to 12 May 2018) and Conference Proceedings Citation Index - Science (CPCI-S) (2014 to 12 May 2018) and Scopus available at the Biomedical Library Gasthuisberg of the Catholic University of Leuven (from inception to 12 May 2018);
- conference abstracts and proceedings on the ISI Web of Knowledge (isiwebofknowledge.com) applying 'SCI-EXPANDED' (2014 to 12 May 2018) and 'CPCI-S' (2014 to 12 May 2018) (Appendix 6);
- LILACS database (searched 12 May 2018) (bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=F) (searched 12 May 2018);
- European grey literature through Open Grey database (searched to 12 May 2018) (www.opengrey.eu/subjects/).

Searching other resources

Two review authors (JB and JK for the first published version, JB and SVW for this update) independently handsearched the reference lists of reviews, guidelines, included and excluded studies, and other related articles for additional eligible studies. One review author (JB) contacted the first or corresponding authors of included studies to ascertain if they were aware of any ongoing or unpublished trials.

Two review authors (JB and JK for the first published version, JB and SVW for this update) independently handsearched the American Society for Reproductive Medicine (ASRM) conference abstracts and proceedings (from 1 January 2014 to 12 May 2018). One review author (JB) contacted European experts and opinion leaders in the field of hysteroscopic surgery to ascertain if these experts were aware of any relevant published or unpublished studies.

Data collection and analysis

Selection of studies

Two or three review authors were responsible for independently selecting the studies (FB and TD for the first published version,

JB, SVW and MB for this update). We scanned titles and abstracts from the searches and obtained the full text of those articles that appeared to be eligible for inclusion. We linked multiple reports of the same study together while citing all the references and indicating the primary reference of the identified study. On assessment, we categorised the trials as 'included studies' ([Characteristics of included studies](#) table), 'excluded studies' ([Characteristics of excluded studies](#) table), 'ongoing studies' ([Characteristics of ongoing studies](#) table) or 'studies awaiting classification' ([Characteristics of studies awaiting classification](#) table). Any disagreements between both review authors who are content experts were resolved through consensus or by a third review author (BWM for the first published version, SW for this update). We contacted the first or corresponding authors of the primary study reports for further clarification when required. If disagreements between review authors were not resolved, we categorised the studies as 'awaiting classification' and reported the disagreement in the final review. We avoided the exclusion of studies on the basis of the reported outcome measures throughout the selection phase by searching all potential eligible studies that could have measured the primary or secondary outcomes even if these were not reported. We appraised studies in an unblinded fashion, as recommended by the CGF Group.

Data extraction and management

Two review authors, one methodologist (JB) and one topic area specialist (SW), independently assessed the studies that appeared to meet the inclusion criteria by using data extraction forms based on the items listed in the protocol of this Cochrane Review ([Appendix 7](#)). We pilot-tested the data extraction form and process by reviewing 10 randomly chosen study reports. In the pilot phase, two review authors consistently identified one retracted record ([Shokeir 2011](#)) on the basis of finding duplicated parts from another study included in the present Cochrane review ([Pérez-Medina 2005](#)). For studies with multiple publications, we used the main trial report as the primary data extraction source and additional details supplemented from secondary papers if applicable. One review author (JB) contacted the first or corresponding authors of the original studies to obtain clarification whenever additional information on trial methodology or original trial data was required. We sent reminder correspondence if a reply was not obtained within two weeks. The two review authors resolved any discrepancies in opinion by discussion; they searched for arbitration by a third review author if consensus was not reached (BWM). One review author (BWM) resolved disagreements which could not be resolved by the review authors after contacting the first or corresponding authors of the primary study reports. If this failed, we reported the disagreement in the review.

Assessment of risk of bias in included studies

Two review authors (JB and SW) independently assessed the risk of bias of the included studies using the Cochrane 'Risk of bias' assessment tool that considers the following criteria, listed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 8, tables 8.5.a and 8.5.b) ([Higgins 2011](#)): random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, completeness of outcome data, selective outcome reporting and other potential sources of bias. We resolved any disagreements by consensus or by discussion with a third review author (BWM). We presented the conclusions in the 'Risk of bias' table ([Characteristics of included studies](#) table), with a full description of all judgements and incorporated them into the interpretation of review findings by means of sensitivity analyses.

We presented a narrative description of the quality of evidence, which is necessary for the interpretation of the results of the review and which is based on the review authors' judgements on the risk of bias of the included trials ([Quality of the evidence](#)).

Measures of treatment effect

For the dichotomous data for live birth, pregnancy, miscarriage and hysteroscopy complications, we used the numbers of events in the control and intervention groups of each study to calculate Mantel-Haenszel odds ratios (OR). We presented 95% confidence intervals (CI) for all outcomes. The OR has mathematically sound properties that are consistent with benefit or harm and which work well in most RCTs on the effectiveness of reproductive surgery given that sample sizes are usually small and trial events are rare. Where data to calculate ORs were not available, we planned to utilise the most detailed numerical data available 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, taking account of legitimate differences. We contacted the corresponding or first authors of all included trials that reported data in a form that was not suitable for meta-analysis, such as time-to-pregnancy (TTP) data. We planned to report the data of those reports that failed to present additional data that could be analysed under 'other data'; we did not include TTP data in any meta-analyses.

Unit of analysis issues

All primary and secondary outcomes were expressed as per woman randomised. In addition, we reported narrative data on miscarriage expressed as per pregnancy as a secondary analysis. We planned to summarise reported data that did not allow a valid analysis, such as 'per cycle', in an additional table without any attempt at meta-analysis. We counted multiple live births and multiple pregnancies as one live birth or one pregnancy event. We planned to include only first-phase data from cross-over trials, if available.

Dealing with missing data

We aimed to analyse the data on an intention-to-treat (ITT) basis. We tried to obtain as much missing data as possible from the original investigators. If this was not possible, we undertook imputation of individual values for the primary outcomes only. We assumed that live births would not have occurred in participants without a reported primary outcome. For all other outcomes, we analysed only the available data. We subjected any imputation of missing data for the primary outcomes to sensitivity analysis. If there were substantial differences in the analysis as compared to an available data analysis, we reported this in the review.

Assessment of heterogeneity

We planned to consider whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary, if more randomised studies were included. We planned to carry out a formal assessment of statistical heterogeneity using the I^2 statistic combined with the Q -statistic. Cochran's Q test, a type of χ^2 statistic, is the classical measure to test significant heterogeneity. Cochran's Q test is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies. The Q -statistic follows χ^2 distribution with $k-1$ degree of freedom where k is the number of studies. Q greater than $k-1$ suggests statistical heterogeneity. A low P value of Cochran's Q test means significant heterogeneous results among different studies; usually, the P value at 0.10 is used as the cut-off. The Q -statistic has low power as a comprehensive test of heterogeneity especially when the number of studies is small. The Q -statistic informs us about the presence or absence of heterogeneity; it does not report on the extent of such heterogeneity. The I^2 statistic describes the percentage of variation across studies that is due to significant heterogeneity rather than random chance. It measures the extent of heterogeneity. An I^2 statistic greater than 50% was taken to indicate substantial heterogeneity (Higgins 2003). We planned to explore possible explanations for heterogeneity by performing sensitivity analyses in Review Manager 5, if there was evidence of substantial statistical heterogeneity (Review Manager 2014).

Assessment of reporting biases

In view of the difficulty in detecting and correcting for publication bias, reporting bias and within-study reporting bias, we planned to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert in identifying duplication of data. We aimed to detect within-trial selective reporting bias, such as trials failing to report obvious outcomes, or reporting them in insufficient detail to allow inclusion. We planned to seek published protocols and to compare the outcomes between the protocol and the final published study report. Where identified studies failed to report the primary outcomes (e.g. live birth), but

did report interim outcomes (e.g. pregnancy), we would have undertaken informal assessment as to whether the interim values were similar to those reported in studies that also reported the primary outcomes. If there were outcomes defined in the protocol or the study report with insufficient data to allow inclusion, the review indicated this lack of data and suggested that further clinical trials need to be conducted to clarify these knowledge gaps. If there were 10 or more studies, we planned to create 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). A gap on either side of the graph would have given a visual indication that some trials had not been identified. Given the low number of studies included in the final review, it was not possible to assess reporting bias formally.

Data synthesis

One review author (JB) entered the data and carried out the statistical analysis of the data using Review Manager 5 (Review Manager 2014). We considered the outcomes live birth and pregnancy to be positive and higher numbers as a benefit. We considered the outcomes miscarriage and hysteroscopy complications in the protocol as negative effects and higher numbers harmful. These aspects were taken into consideration when assessing the summary graphs. In the quantitative synthesis an increase in the odds of a particular outcome, either beneficial or harmful, was displayed graphically to the right of the centre-line and a decrease in the odds of an outcome to the left of the centre-line.

We planned to combine data from primary studies in a meta-analysis with Review Manager 5 using the Peto method and a fixed-effect model (Higgins 2011) for the following comparisons, if more randomised studies could have been included and if significant clinical diversity and statistical heterogeneity could have been confidently ruled out.

- Operative hysteroscopy versus control in women with otherwise unexplained subfertility and suspected major uterine cavity abnormalities diagnosed by US, SIS, GIS, HSG, diagnostic hysteroscopy or any combination of these methods.
- Operative hysteroscopy versus control in women undergoing MAR with suspected major uterine cavity abnormalities diagnosed by US, SIS, GIS, HSG, diagnostic hysteroscopy or any combination of these methods.

We planned to define analyses that were both comprehensive and mutually exclusive so that all eligible study results were slotted into one of the two predefined strata only. If there were no retrieved trials for some comparisons, the review indicated their absence identifying knowledge gaps which need further research. Since meta-analysis was not possible due to the limited number of studies included in the review, we presented a narrative overview as pre-specified in the protocol).

Subgroup analysis and investigation of heterogeneity

We planned to carry out subgroup analyses to determine the separate evidence within the following subgroups, if enough data were available.

- Those studies that reported 'live birth' and 'ongoing or clinical pregnancy' to assess any overestimation of effect and reporting bias.
- For the two types of randomised comparison, stratified according to the type of uterine abnormality, we planned to carry out subgroup analyses according to the extent or severity of the uterine abnormality. We used the length and diameter in centimetres or calculated volumes of endometrial polyps and submucous fibroids, the lengths and widths of uterine septa and the European Society of Gynaecological Endoscopy (ESGE) classification for intrauterine adhesions as references when applicable (Wamsteker 1998).
- We planned to carry out subgroup analyses based on the modifier participant age if enough studies were available.

The interpretation of the statistical analysis for subgroups is not without problems. In the final review, we reported the interpretation of any subgroup analysis performed restrictively, if at all possible, and with utmost caution even if enough data were retrieved.

Sensitivity analysis

We aimed to perform sensitivity analyses for the primary outcomes to determine whether the conclusions are robust to arbitrary decisions made regarding the eligibility and analysis. These analyses included consideration of whether conclusions would have differed if:

- eligibility was restricted to studies at low risk of bias in all domains;
- alternative imputation strategies were adopted;
- a random-effects rather than a fixed-effect model was adopted;
- the summary effect measure was risk ratio rather than OR.

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

We prepared 'summary of findings' tables using GRADE and Cochrane methods (GRADEpro GDT; Higgins 2011). These tables evaluated the overall quality of the body of evidence for the main review outcomes (primary outcome of effectiveness - live birth - as well as secondary outcome of effectiveness - clinical pregnancy - and the adverse events - hysteroscopy complication and miscarriage) for the two main review comparisons (randomised comparison between operative hysteroscopy versus control for unexplained subfertility associated with suspected major uterine cavity abnormalities and randomised comparison between operative

hysteroscopy versus control for suspected major uterine cavity abnormalities prior to MAR). We assessed the quality of the evidence using GRADE criteria: risk of bias, consistency of effect, imprecision, indirectness and publication bias). Two review authors independently made judgements about evidence quality (high, moderate, low or very low), with disagreements resolved by discussion. Judgements were justified, documented, and incorporated into reporting of results for each outcome.

RESULTS

Description of studies

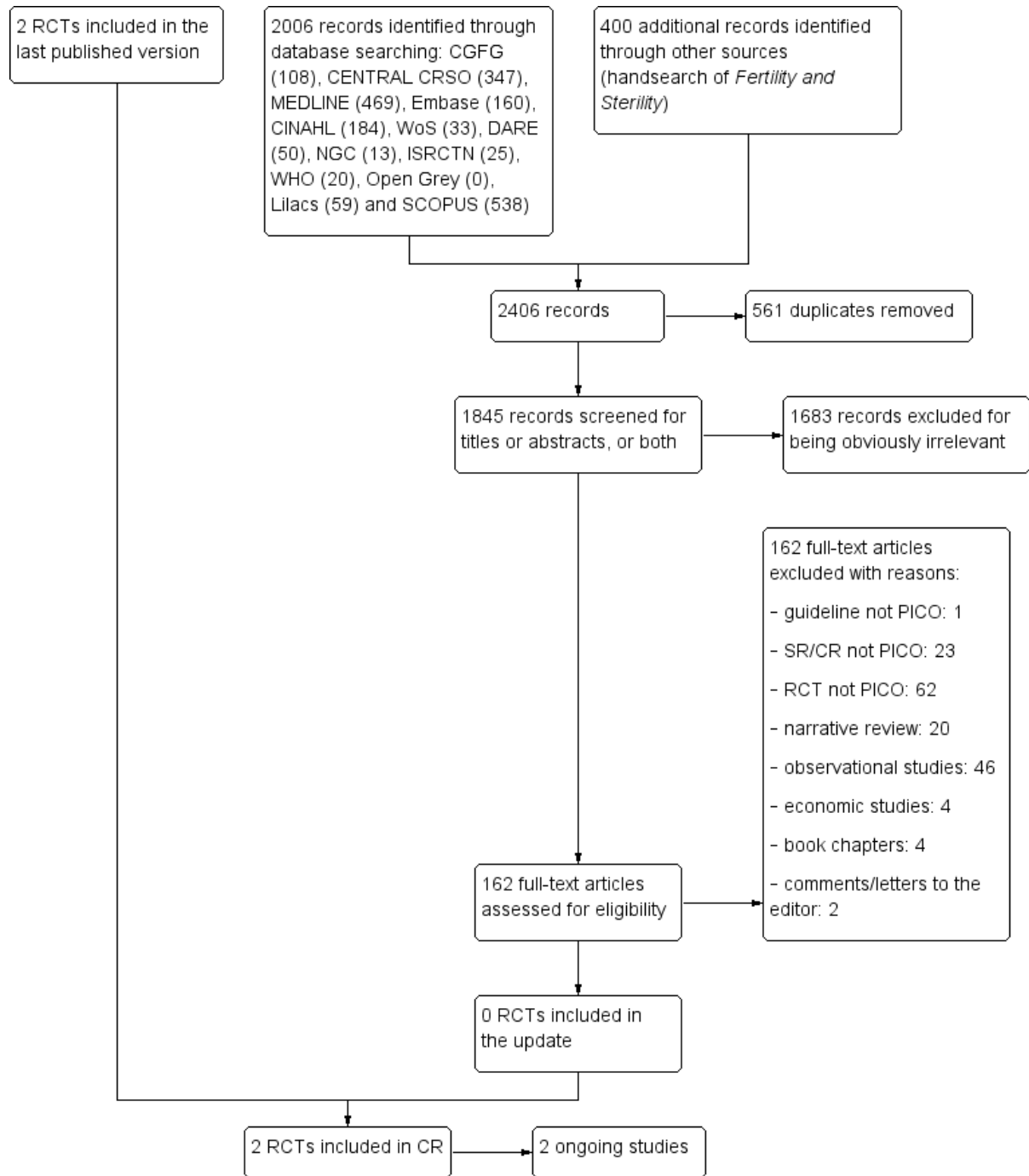
See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#); [Characteristics of ongoing studies](#) tables.

Results of the search

For the present update, there were 108 records from the CGFG Specialised Register, 347 records from CRSO, 469 from MEDLINE, 160 from Embase and 33 from Web of Science. An electronic search in DARE produced 50 records; there were 13 guidelines from National Guideline Clearinghouse, 25 records from the ISRCTN register of controlled trials and 20 records from WHO ICTRP. We identified 538 additional references in Scopus. We identified 184 records in CINAHL and 59 records in LILACS but none in Open Grey. We handsearched 400 abstracts in the congress proceedings of the ASRM for the period 2014 to 2018; we identified no additional abstracts after contacting the experts of the European Society for Gynaecological Endoscopy (ESGE). After combining 2006 records identified from electronic searches with 400 additional records through handsearching, we screened 2406 records for duplicates by using a specialised software program (EndNote Web). After the removal of 561 duplicate references, we screened the titles or abstracts, or both of 1845 records. We removed 1683 records that were obviously irrelevant. We assessed 162 full-text articles for eligibility. We did not include additional RCTs in the updated version, so finally we included two RCTs addressing the research questions of this Cochrane Review ([Characteristics of included studies](#) table). We excluded 64 studies for various reasons ([Characteristics of excluded studies](#) table); 58 studies did not address the PICO research questions of this Cochrane Review, four studies were not randomised, one was a quasi-randomised trial and one potentially eligible RCT was excluded (Shokeir 2010) because the study report had been retracted at the request of the publisher. Two trials are still ongoing ([Characteristics of ongoing studies](#) table).

See: PRISMA flow chart ([Figure 1](#)).

Figure 1. Study flow diagram: summary of searches since 2014. CR: Cochrane Review; PICO: Population, Intervention, Comparator, Outcome; RCT: randomised controlled trial; SR: systematic review.



Included studies

Study design and setting

The review included two parallel-design RCTs. Both were single-centre studies, one conducted in Italy (Casini 2006) and the other in Spain (Pérez-Medina 2005).

Participants

One study included 94 women with submucous fibroids with or without intramural fibroids and otherwise unexplained subfertility (Casini 2006). There were 52 women in the intervention group and 42 women in the control group. The mean participant age was 31 years (range 29 to 34) in the subgroup of women with submucous fibroids only and 32 years (range 30 to 35) in the subgroup of women with mixed intramural-submucous fibroids. All women underwent a complete fertility assessment. The presence of uterine fibroids was by TVS. All women who were affected by uterine fibroids excluding all other causes of infertility were asked to participate in the study. Only women aged 35 years or less with a problem of subfertility for at least one year and the presence of one fibroid of diameter 40 mm or less were selected for randomisation. Women older than 35 years or with other causes of infertility at the performed examinations were excluded. Other exclusion criteria were the presence of two or more fibroids of diameter greater than 40 mm; body weight greater than 20% of normal weight; and use of medication containing oestrogens, progestins or androgens in the eight weeks prior to the study.

The second study included 215 women with unexplained, male or female factor infertility for at least 24 months bound to undergo IUI with a sonographic diagnosis of endometrial polyps (Pérez-Medina 2005). 11 women were lost to follow-up, six in the intervention group and five in the control group. Data from 101 women in the intervention group and 103 women in the control group were available for analysis. The mean participant age was 31 years (range 27 to 35). All women experienced primary subfertility; they all underwent a complete fertility assessment. Unexplained infertility was diagnosed in women with normal ovulatory cycles, semen analysis, HSG and postcoital testing. Female factor infertility was diagnosed in women with ovulatory dysfunction, cervical factor or endometriosis. Male factor infertility was diagnosed if two semen analyses obtained at least one month apart were subnormal according to the WHO criteria. The sonographic diagnosis of endometrial polyps was established by the demonstration of the vascular stalk of the endometrial polyp by colour Doppler in a hyperechogenic formation with regular contours occupying the uterine cavity, surrounded by a small hypoechogenic

halo. Women older than 39 years of age or with anovulation or uncorrected tubal disease or previous unsuccessful use of recombinant follicle-stimulating hormone (FSH), as well as women with a male partner with azoospermia, were excluded from randomisation.

For details of the inclusion and exclusion criteria, see [Characteristics of included studies](#) table.

Interventions

One trial treated the intervention group with hysteroscopic surgery to remove the fibroids; TVS was done three months after the procedure (Casini 2006). Women in the intervention group were suggested to abstain from sexual intercourse for three months and then to start having regular fertility-oriented intercourse. Women in the control group were asked to immediately start having fertility-oriented intercourse. Both groups were monitored for up to 12 months after study commencement.

The second trial performed all hysteroscopic interventions in an outpatient clinic setting under local anaesthesia by one gynaecologist (Pérez-Medina 2005). In the intervention group, the endometrial polyps suspected on Doppler US were extracted by means of rigid 1.5 mm scissors and forceps through the working channel of a 5.5 mm continuous flow hysteroscope. All removed polyps were submitted for histopathological examination. If resection was not possible during the outpatient hysteroscopy, the woman was scheduled for operative hysteroscopy under spinal anaesthesia in the operating theatre of the hospital. All the hysteroscopic interventions were done in the follicular phase of the menstrual cycle. The women of the intervention group were scheduled to receive four cycles of IUI, using subcutaneous injections of FSH 50 IU (international units) daily from the third day of the cycle. The first IUI treatment cycle was started three cycles after the operative hysteroscopy. In the control group, the endometrial polyps suspected on Doppler US were left in place during diagnostic hysteroscopy using a 5.5 mm continuous flow hysteroscope; polyp biopsy was performed to establish a histopathological diagnosis. All women in the control group were scheduled to receive four cycles of IUI, using subcutaneous injections of FSH 50 IU daily from the third day of the cycle. The first IUI treatment cycle was scheduled three cycles after the diagnostic hysteroscopy. Four IUI cycles were attempted before finishing the trial.

Outcomes

Neither of the two included studies reported data on the primary outcomes for this review, live birth and hysteroscopy complication rates.

The first trial measured two secondary outcomes, clinical pregnancy and miscarriage rate (Casini 2006). A clinical pregnancy

was defined by the visualisation of an embryo with cardiac activity at six to seven weeks of pregnancy. Miscarriage was defined by the loss of an intrauterine pregnancy between the seventh and 12th weeks of gestation.

The second trial reported only one secondary outcome, the clinical pregnancy rate (Pérez-Medina 2005). This was defined by a pregnancy diagnosed by US visualisation of one or more gestational sacs.

The authors of one study gave a plausible explanation for the failure to report on the live birth rate (Pérez-Medina 2005). They failed to give an explanation for the lack of data on the other primary outcome, the hysteroscopy complication rate. The study authors of the other trial could not be contacted successfully for further clarification on the absence of reporting the primary outcomes (Casini 2006).

Excluded studies

We excluded 64 studies on hysteroscopic interventions for various reasons.

- One randomised trial (Shokeir 2010) was excluded since the main published report was retracted at the request of the editor of the publishing journal as it duplicated parts of a paper on a different topic that had already appeared in another journal published years before (Pérez-Medina 2005).

- One trial was a quasi-randomised trial (Pabuccu 2008).
- Four trials were non-randomised studies (De Angelis 2010; Gao 2013; Mohammed 2014; Trninić -Pjević 2011).

- Fifty-eight randomised trials did not address the prespecified PICO (Participants, Interventions, Comparisons and Outcomes) research questions of this Cochrane Review.

- Fourteen trials studied the effectiveness of hysteroscopy in subfertile women bound to undergo IVF or ICSI treatment with unsuspected or no uterine cavity abnormalities (Abiri 2014; Aghahosseini 2012; Aleyassin 2017; Basma 2013; Demiroglu 2004; Di Florio 2013; El-Nashar 2011; Elsetohy 2015; El-Toukhy 2009; Fatemi 2007; Rama Raju 2006; Shawki 2012; Smit 2016; Sohrabvand 2012).

- One trial assessed the effectiveness of hysteroscopy prior to IUI in women with no previously detected uterine anomalies (Moramezi 2012).

- Three trials assessed the effectiveness of endometrial injury (El-Khayat 2015; Hare 2013; Weiss 2005).

- Twelve trials had a study population that included women who were not of reproductive age experiencing gynaecological problems other than subfertility (Clark 2015; Hamerlynck 2015; Javidan 2017; Kamel 2014; Lara-Dominguez 2016; Lieng 2010a; Muzii 2007; Muzii 2017; Nappi 2013; Rubino 2015; Smith 2014; van Dongen 2008).

- Two trials had a study population that included only women with repeated miscarriage (Vercellini 1993) or recurrent implantation failure (Cao 2018).

- Eighteen trials studied the effectiveness of adjunctive therapies (hyaluronic acid gel, amnion graft, balloon catheter, cyclical hormone replacement therapy alone or intrauterine device alone or both cotreatments combined, autologous platelet rich plasma) for the prevention of intrauterine adhesions following hysteroscopic adhesiolysis (Abu Rafea 2013; Acunzo 2003; Aghajanova 2018; Amer 2010; De Iaco 2003; Di Spiezo Sardo 2011; Fuchs 2014; Gan 2017; Guida 2004; Guo 2017; Hanstede 2016; Lin 2014; Liu 2016; Paz 2014; Revel 2011; Roy 2014; Tonguc 2010; Xiao 2015).

- Six trials compared different surgical techniques for treating uterine septum in a mixed study population of women with subfertility or recurrent pregnancy loss (Colacurci 2007; Darwish 2009; Parsanezhad 2006; Roy 2015; Roy 2017; Youssef 2013).

- One trial assessed the interobserver agreement of gynaecologists performing hysteroscopy for a septate uterus who received instructions on the assessment of the septum prior to the procedure versus gynaecologists who did not (Smit 2015).

- One trial was an RCT investigating the effects of mindfulness-based stress reduction on anxiety, depression and quality of life in women with intrauterine adhesions (Chen 2017).

See: [Characteristics of excluded studies](#) table.

Studies awaiting classification

We found no studies awaiting classification.

Ongoing studies

We retrieved two ongoing studies (SEPTUM trial; TRUST trial). The TRUST trial is a multicentre RCT. The starting date was 1 October 2008. The sample size of this study is 68 women; on 4 May 2018 the 63rd participant was included.

The SEPTUM trial was designed as a pilot multicentre RCT to assess the feasibility for a larger adequately powered trial. The trial is closed to further recruitment due to feasibility issues with recruitment. Six participants were included and will be followed up for 24 months post intervention (personal correspondence with Dr Matthew Prior).

See: [Characteristics of ongoing studies](#) table.

Risk of bias in included studies

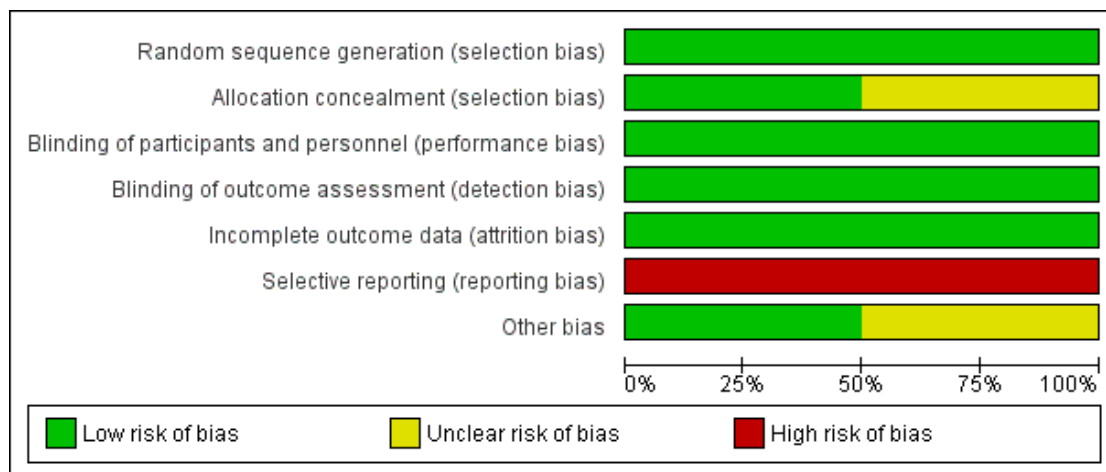
See the 'Risk of bias' summary for the review authors' judgements about each risk of bias item in the included study (Figure 2).

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Casini 2006	+	?	+	+	+	-	?
Pérez-Medina 2005	+	+	+	+	+	-	+

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



Allocation

We judged both studies at low risk of selection bias related to random sequence generation, as both used computerised random numbers tables (Casini 2006; Pérez-Medina 2005).

We judged one study at low risk for selection bias related to allocation concealment, as they used sequentially numbered, opaque, sealed envelopes to conceal the random allocation of women to one of the comparison groups (Pérez-Medina 2005). We judged the second trial at unclear risk for selection bias related to allocation concealment since the method used was not reported and no further clarification by the authors could be obtained (Casini 2006).

Blinding

We judged both studies at low risk of performance and detection bias since both surgical studies had unequivocal outcomes that are most likely not affected by unclear blinding of participants, personnel and outcome assessors (Casini 2006; Pérez-Medina 2005). The methods were not reported and no further clarification could be obtained.

Incomplete outcome data

We judged both studies at low risk of attrition bias. One study reported outcome data of all randomised women (Casini 2006). The second study analysed the majority of women randomised (95%) (Pérez-Medina 2005). The missing outcome data in the remaining 5% were balanced in numbers with similar reasons for missing data between the two comparison groups.

Selective reporting

We judged both studies at high risk of reporting bias (Casini 2006; Pérez-Medina 2005). Both studies failed to include data for the primary outcome live birth, which could reasonably have been reported in studies conducted over a seven-year (Casini 2006) and a four-year (Pérez-Medina 2005) period. Although a plausible explanation was given by the contact author of one study (Pérez-Medina 2005), we judged that it could have been possible to obtain data on the live birth rates if the study authors had contacted the referring gynaecologists (see Characteristics of included studies table). Moreover, one trial reported no data on adverse outcomes such as miscarriage or hysteroscopy complications (Pérez-Medina 2005), whereas the second study reported miscarriage rates only for the adverse events (Casini 2006).

Other potential sources of bias

We judged one study to be at unclear risk of other potential sources of bias (Casini 2006). The study did not report the mean ages and duration of infertility in the intervention and control group of women with submucous fibroids; we were unable to obtain these data from the study authors given that we were unsuccessful in contacting them. It is unclear whether this might have caused imbalance in the baseline characteristics between the comparison groups in this randomised trial (Casini 2006). Moreover, it was unclear whether hysteroscopy had been performed in all participants to confirm the position of the ultrasonically detected fibroids. We judged the second study at low risk of other potential sources of bias since there was no evidence of baseline imbalance in the participant characteristics between the two comparison groups (Pérez-Medina 2005).

Publication bias could not be formally assessed due to the very limited number of studies included in this Cochrane Review.

Primary outcomes

Effects of interventions

See: [Summary of findings for the main comparison](#) Operative hysteroscopy versus control in women with otherwise unexplained subfertility and suspected major uterine cavity abnormalities; [Summary of findings 2](#) Operative hysteroscopy versus control in women undergoing medically assisted reproduction with suspected major uterine cavity abnormalities

I. Operative hysteroscopy versus control in women with otherwise unexplained subfertility and suspected major uterine cavity abnormalities

See: [Summary of findings for the main comparison](#).

Endometrial polyps

The search identified no studies on endometrial polyps.

Submucous fibroids

One study compared hysteroscopic myomectomy versus no surgery in women with unexplained subfertility and submucous fibroids only or combined with intramural fibroids (Casini 2006).

Live birth

There were no data for live births.

Adverse events: hysteroscopy complications

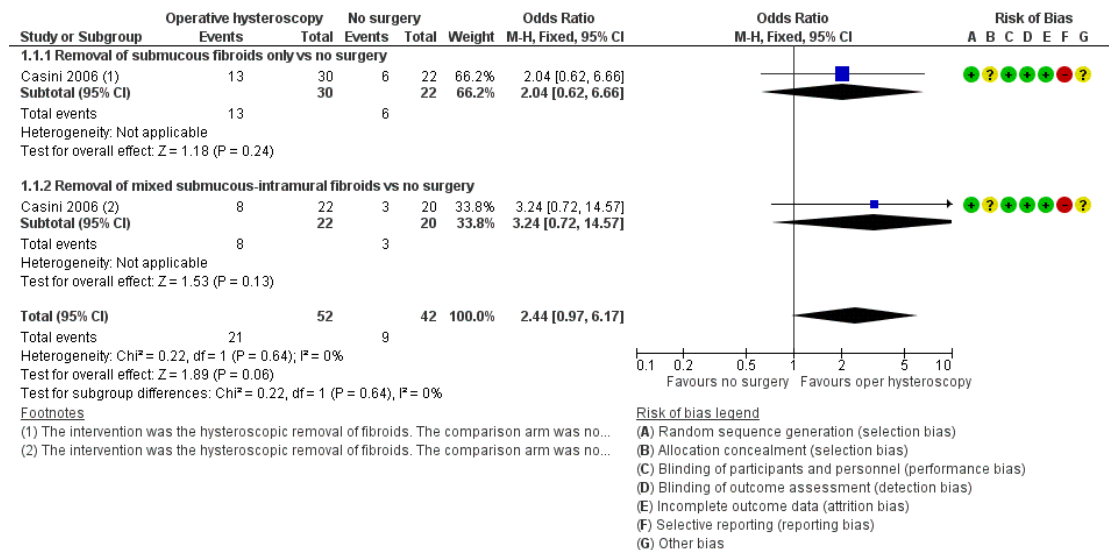
There were no data for hysteroscopy complications.

Secondary outcomes

Clinical pregnancy

In women with otherwise unexplained subfertility and submucous fibroids, we were uncertain whether hysteroscopic myomectomy improved the clinical pregnancy rate compared to expectant management (OR 2.44, 95% CI 0.97 to 6.17; $P = 0.06$, 94 women; [Analysis 1.1](#); [Figure 4](#)).

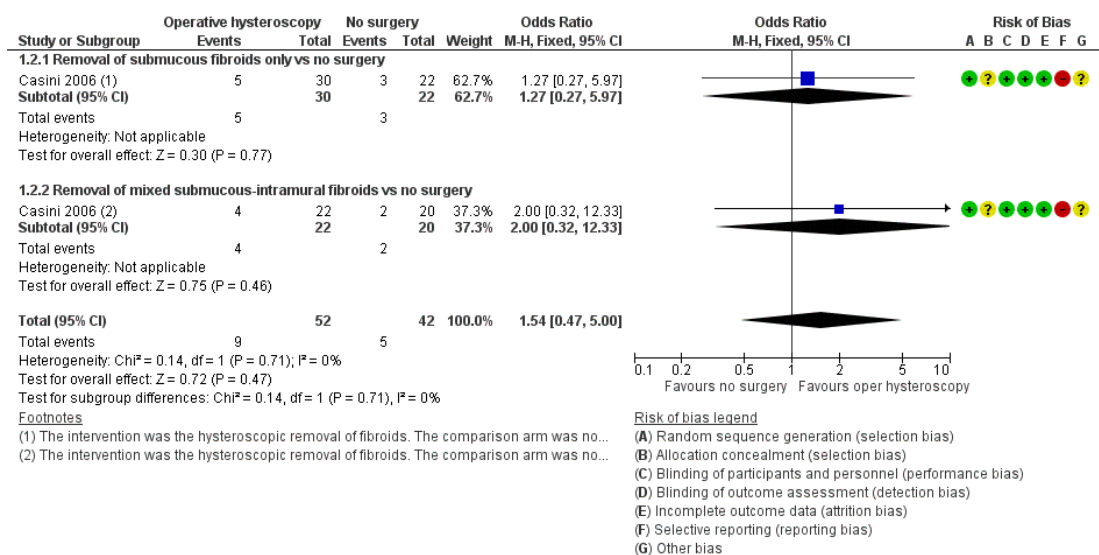
Figure 4. Forest plot of comparison: I Hysteroscopic myomectomy vs no surgery in women with unexplained subfertility and submucous fibroids. Outcome: I.1 Clinical pregnancy per woman randomised.



Adverse events: miscarriage

There was insufficient evidence to determine whether there was a difference between the removal of one submucous fibroid of diameter 40 mm or less in women with otherwise unexplained subfertility for at least one year versus expectant management for the outcome of miscarriage per woman randomised (OR 1.54, 95% CI 0.47 to 5.00; $P = 0.47$, 94 women; Analysis 1.2; Figure 5). As a secondary analysis, we reported the miscarriage rate per clinical pregnancy. There was insufficient evidence to determine whether there was a difference between the groups (OR 0.58, 95% CI 0.12 to 2.85; $P = 0.50$, 30 clinical pregnancies in 94 women).

Figure 5. Forest plot of comparison: 1 Hysteroscopic myomectomy vs no surgery in women with unexplained subfertility and submucous fibroids. Outcome: 1.2 Miscarriage per clinical pregnancy.



Subgroup analyses

We performed no subgroup analyses across studies to assess any overestimation of treatment effect or reporting bias, due to the limited number of studies.

One prespecified subgroup analysis within the trial was done for the two secondary outcomes of clinical pregnancy and miscarriage according to whether submucous fibroids only or mixed submucous-intramural fibroids were considered. There was insufficient evidence to determine whether there was a difference for the secondary outcome clinical pregnancy between the 'submucous only' subgroup (OR 2.04, 95% CI 0.62 to 6.66; $P = 0.24$, 1 RCT, 52 women) and the 'mixed submucous-intramural' subgroup (OR

3.24, 95% CI 0.72 to 14.57; $P = 0.13$, 1 RCT, 42 women); the tests for subgroup differences demonstrated no statistical heterogeneity beyond chance ($Chi^2 = 0.22$, degrees of freedom (df) = 1; $P = 0.64$, $I^2 = 0\%$). There was insufficient evidence to determine whether there was a difference for the secondary outcome miscarriage between the 'submucous only' subgroup (OR 0.63, 95% CI 0.09 to 4.40; $P = 0.64$, 1 RCT, 19 clinical pregnancies in 52 women) and the 'mixed submucous-intramural' subgroup (OR 0.50, 95% CI 0.03 to 7.99; $P = 0.62$, 1 RCT, 11 clinical pregnancies in 42 women); the tests for subgroup differences demonstrated no statistical heterogeneity beyond chance ($Chi^2 = 0.02$, $df = 1$, $P = 0.90$, $I^2 = 0\%$).

Uterine septum

There were no data for uterine septum.

Intrauterine adhesions

There were no data for intrauterine adhesions.

2. Operative hysteroscopy versus control in women undergoing medically assisted reproduction with suspected major uterine cavity abnormalities

See: [Summary of findings 2](#).

Endometrial polyps prior to intrauterine insemination

One study compared hysteroscopic removal of polyps versus diagnostic hysteroscopy and polyp biopsy in women with endometrial polyps undergoing gonadotropin treatment and IUI ([Pérez-Medina 2005](#)).

Primary outcomes

Live birth

There were no data for live births.

Adverse events: hysteroscopy complications

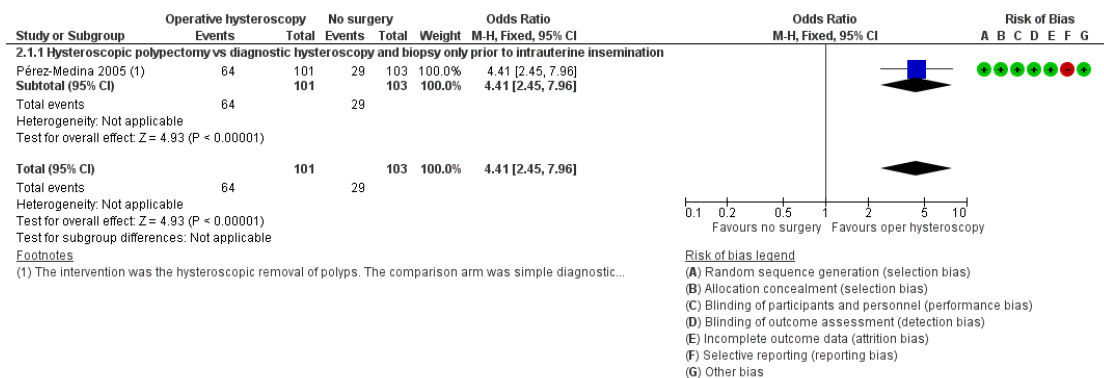
There were no data for hysteroscopy complications.

Secondary outcomes

Clinical pregnancy

The hysteroscopic removal of polyps prior to IUI may have improved the clinical pregnancy rate compared to diagnostic hysteroscopy only: if 28% of women achieved a clinical pregnancy without polyp removal, the evidence suggested that 63% of women (95% CI 45% to 89%) would have achieved a clinical pregnancy after the hysteroscopic removal of the endometrial polyps (OR 4.41, 95% CI 2.45 to 7.96; $P < 0.00001$, 204 women; [Analysis 2.1](#); [Figure 6](#)). The number needed to treat for an additional beneficial outcome was 3 (95% CI 2 to 4).

Figure 6. Forest plot of comparison: 2 Hysteroscopic removal of polyps vs diagnostic hysteroscopy and biopsy only prior to intrauterine insemination. Outcome: 2.1 Clinical pregnancy per woman randomised.



Adverse events: miscarriage

There were no data for miscarriage.

Subgroup analyses

We performed no subgroup analyses across studies to assess any overestimation of treatment effect or reporting bias given the limited number of studies.

We performed the following two subgroup analyses within the included study.

A first prespecified subgroup analysis studied the effect of polyp size on the secondary outcome of clinical pregnancy. On histopatho-

logical examination, the mean size of the polyps removed was 16 mm (range 3 mm to 24 mm). The primary study examined the effect of polyp size on the clinical pregnancy rate in the intervention group. They analysed the data based on the size of the removed polyps, subdivided into four groups based in their quartiles (less than 5 mm, 5 mm to 10 mm, 11 mm to 20 mm and greater than 20 mm); there was insufficient evidence to determine whether there was a difference between these four subgroups given the limited number of data ($P = 0.32$) (Table 1). There was no evidence of an effect of polyp size on the outcome of clinical pregnancy, but these results should be interpreted carefully given the limited numbers in only one included study. There were no data on the estimated size of the polyps in the control group.

The second subgroup analysis studied the effect of the timing of the IUI treatment after hysteroscopy on the secondary outcome clinical pregnancy. About 29% of women in the polypectomy group, compared to 3% in the diagnostic hysteroscopy group, became pregnant in the three-month period after the hysteroscopy before the treatment with gonadotropin and IUI was started; this was calculated from the Kaplan-Meier survival analysis in the published report of the primary study (Pérez-Medina 2005). Hysteroscopic polypectomy may have improved the clinical pregnancy rate compared to diagnostic hysteroscopy and polyp biopsy in women waiting to be treated with gonadotropin and IUI (OR 13, 95% CI 3.9 to 46; $P < 0.0001$, 1 study, 204 women; available-data analysis). The number needed to treat to for an additional beneficial outcome after hysteroscopic polypectomy while waiting for further treatment with gonadotropin and IUI was 4 (95% CI 3 to 6). In women who started gonadotropin and IUI treatment the pregnancy rates per woman were 49% in the intervention group and 26% in the control group, calculated from data in the published report of the primary study (Pérez-Medina 2005). Hysteroscopic polypectomy may have improved the clinical pregnancy rate in women who started from three months after the surgical procedure with gonadotropin and IUI treatment (OR 2.7, 95% CI 1.4 to 5.1; $P = 0.003$, 1 RCT, 172 women; available-data analysis). The number needed to treat for an additional beneficial outcome when treated with gonadotropin and IUI after a prior hysteroscopic polypectomy was 4 (95% CI 3 to 12). This was a post hoc subgroup analysis. Quoting from the primary study published report “A second important conclusion in our study is that pregnancies after polypectomy are frequently obtained spontaneously while waiting for the treatment, suggesting a strong cause-effect of the polyp in the implantation process. This led us to defer the first IUI to three menstrual cycles after the polypectomy is per-

formed. Longer series are needed to verify these results”. Data from this subgroup analysis should be treated with caution as subgroup analysis by itself is observational in nature, and statistical interpretation of its results is not without problems.

Sensitivity analyses

A sensitivity analysis comparing an ITT analysis assuming that clinical pregnancies would not have occurred in participants with missing data, rather than an available-data analysis, did not affect the statistical significance of the main analysis for the secondary outcome clinical pregnancy (OR 4.0, 95% CI 2.3 to 7.2; $P < 0.00001$; 1 RCT, 215 women randomised). No other imputation strategies for dealing with the missing data were assumed given the limited number of studies.

Endometrial polyps prior to in vitro fertilisation or intracytoplasmic sperm injection

We found no studies on endometrial polyps prior to IVF or ICSI.

Submucous fibroids prior to intrauterine insemination, in vitro fertilisation or intracytoplasmic sperm injection

We found no studies on submucous fibroids prior to IUI, IVF or ICSI.

Uterine septum prior to intrauterine insemination, in vitro fertilisation or intracytoplasmic sperm injection

We found no studies on uterine septum prior to IUI, IVF or ICSI.

Intrauterine adhesions prior to intrauterine insemination, in vitro fertilisation or intracytoplasmic sperm injection

We found no studies on intrauterine adhesions prior to IUI, IVF or ICSI.

Other analyses

We planned to do sensitivity analyses for Analysis 1.1; Analysis 1.2; and Analysis 2.1 to consider whether conclusions would have differed if eligibility had been restricted to studies at low risk of bias in all domains. We retrieved only one study for each random comparison. Moreover for both studies there was at least one item at high risk of bias (Figure 2). Hence no sensitivity analyses were performed in the present updated Cochrane Review.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Operative hysteroscopy versus control in women undergoing medically assisted reproduction with suspected major uterine cavity abnormalities						
<p>Patient or population: subfertile women with endometrial polyps diagnosed by ultrasonography prior to treatment with gonadotropin and intrauterine insemination</p> <p>Settings: infertility unit of a university tertiary hospital in Madrid, Spain</p> <p>Intervention: hysteroscopic polypectomy using a 5.5 mm continuous flow office hysteroscope with a 1.5 mm scissors and forceps</p> <p>Comparison: diagnostic hysteroscopy using a 5.5 mm continuous flow office hysteroscope and polyp biopsy</p>						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Polypectomy				
Live birth	No data reported.					
Adverse events: hysteroscopy complications	No data reported.					
Clinical pregnancy^d Ultrasound 4 intrauterine insemination cycles	282 per 1000	634 per 1000 (451 to 894)	OR 4.41 (2.45 to 7.96)	204 (1 study)	⊕⊕○○ Low^{b,c}	-
Adverse events: miscarriage	No data were reported for this secondary outcome.					

* The basis for the **assumed risk** is the control group risk of the single included study (Pérez-Medina 2005). 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.

^aClinical pregnancy was defined by the presence of at least one gestational sac on ultrasound.

^bDowngraded by one level for serious risk of bias (high risk for selective outcome reporting).

^cDowngraded by one level for serious imprecision (wide confidence interval of the effect size estimate).

DISCUSSION

Summary of main results

This systematic review aimed to investigate whether the hysteroscopic treatment of suspected major uterine cavity abnormalities made a difference to the main outcomes of live birth or pregnancy and the adverse events (hysteroscopy complications and miscarriage) in subfertile women with otherwise unexplained subfertility or before IUI, IVF or ICSI. We searched for studies on two randomised comparisons to study the effectiveness of operative hysteroscopy in the treatment of subfertility associated with major uterine cavity abnormalities.

The first randomised comparison was operative hysteroscopy versus control in women with otherwise unexplained subfertility and suspected major uterine cavity abnormalities - stratified into endometrial polyps, submucous fibroids, intrauterine adhesions or septate uterus - diagnosed by US, SIS/GIS, HSG, diagnostic hysteroscopy or any combination of these methods ([Summary of findings for the main comparison](#)). We retrieved and critically appraised only one trial in this category comparing the hysteroscopic removal of one submucous fibroid with a diameter of 40 mm or less in women aged 35 years or less with otherwise unexplained subfertility versus expectant management (no surgery followed by fertility-oriented intercourse) ([Casini 2006](#)). There was insufficient evidence to determine whether there was a difference between groups. This may have been due to a type II error: we calculated that a sample size of 91 participants was needed to detect a difference of 19% for the outcome of clinical pregnancy between groups with a statistical power of 80% at a confidence level of 95% ($\alpha = 0.05$ and $\beta = 0.20$). In other words, a study population of at least 182 participants is needed to detect any statistically significant difference if present; compared to only 94 women in the study ([Casini 2006](#)). There was insufficient evidence to determine whether there was a difference between groups for the miscarriage rate. We found no data on live birth or hysteroscopy complication rates. We found no studies in women with endometrial polyps, intrauterine adhesions or septate uterus for this randomised comparison.

The second randomised comparison was operative hysteroscopy versus control in women undergoing MAR - stratified into IUI, IVF or ICSI - with suspected major uterine cavity abnormalities - stratified into endometrial polyps, submucous fibroids, intrauterine adhesions or septate uterus - diagnosed by US, SIS, GIS, HSG, diagnostic hysteroscopy or any combination of these methods ([Summary of findings 2](#)). We retrieved and critically appraised one trial in this category randomly comparing hysteroscopic polypectomy versus diagnostic hysteroscopy comparison in subfertile women with suspected endometrial polyps bound to undergo IUI ([Pérez-Medina 2005](#)). The hysteroscopic removal of polyps with a mean size of 16 mm (range 3 mm to 24 mm) may have improved clinical pregnancy rates compared to simple diagnostic hysteroscopy. A sensitivity analysis on the choice to use

an ITT analysis by making the imputation that clinical pregnancies would not have occurred in participants with missing data rather than an available-data analysis did not demonstrate an impact on the overall results. We found no data for live birth, hysteroscopy complication or miscarriage rates. The increase in clinical pregnancy rates following hysteroscopic polypectomy was due to a higher proportion of spontaneous conceptions before starting IUI and a higher chance of conceiving after starting gonadotropin treatment and IUI. The results of this post hoc subgroup analysis should be interpreted with caution. We found no studies in women with submucous fibroids, intrauterine adhesions or septate uterus prior to IUI or in women with all types of suspected uterine cavity abnormalities prior to IVF or ICSI.

Due to the lack of studies, there was no formal assessment of publication bias.

Overall completeness and applicability of evidence

Evidence on the effectiveness of treating suspected major uterine cavity abnormalities by operative hysteroscopy compared to a control intervention in women with otherwise unexplained subfertility was insufficient. We found no trials on the hysteroscopic treatment of endometrial polyps, intrauterine adhesions or uterine septum compared to a control intervention in women with otherwise unexplained subfertility. The only included study in this category failed to report on the primary outcomes for this review. Evidence on the effectiveness of operative hysteroscopy compared to control in subfertile women with associated major uterine cavity abnormalities prior to MAR was incomplete since data had been found only for subfertile women with suspected endometrial polyps prior to IUI. The search found no data on the effectiveness of operative hysteroscopy versus control in subfertile women with other suspected major cavity abnormalities such as submucous fibroids, intrauterine adhesions or uterine septum prior to IUI or other techniques such as IVF or ICSI for all outcomes. Moreover, for the randomised comparison of hysteroscopic polypectomy versus diagnostic hysteroscopy prior to IUI, there were no data available for the primary outcomes. The evidence retrieved was by consequence insufficient to address all the objectives of the present Cochrane Review.

The uncertainty of whether there were differences between the comparison groups in the trial of hysteroscopic myomectomy in women with submucous fibroids and otherwise unexplained subfertility did not exclude a clinically relevant benefit with the hysteroscopic removal of fibroids. It is generally accepted that submucous fibroids are very likely to interfere with normal fertility ([Pritts 2001](#); [Pritts 2009](#)). In everyday practice, most skilled hysteroscopic surgeons will counsel women with submucous fibroids associated with otherwise unexplained subfertility or bound to be treated with IUI, IVF or ICSI to have the submucous fibroids removed before further expectant management or MAR; besides of

fering participation in a pragmatic RCT on this topic there seems no other sound clinical alternative.

Although the results of the trial on hysteroscopic polypectomy are relevant for everyday practice (Pérez-Medina 2005), one-third of the randomised women treated by IUI had an ovulatory disorder other than anovulation. In everyday clinical practice, ovulatory disorder is by itself not an indication for IUI as opposed to male factor (Bensdorp 2007) and unexplained subfertility (Veltman-Verhulst 2012). We have considered doing a sensitivity analysis to determine if the inclusion and exclusion of women with ovulatory disorders could have influenced the magnitude of the treatment effect but failed to obtain the data from the study authors.

Quality of the evidence

See Table 2; Table 3; Summary of findings for the main comparison; Summary of findings 2.

The present review included only two trials; neither reported the primary outcomes live birth or hysteroscopy complications.

We graded the evidence using the GRADE tool (GRADEpro GDT) of the trial on hysteroscopic myomectomy as very low (Casini 2006). It was a small study with few events. We downgraded by two levels for very serious risk of bias: there was uncertainty about allocation concealment, it was unclear whether there was imbalance in the baseline characteristics of the study groups and there was a high risk of selective outcome reporting. Moreover, we downgraded by one level for serious imprecision given the wide CIs of the point estimate of the treatment effect.

We graded the evidence of the trial on hysteroscopic polypectomy as low (Pérez-Medina 2005): we downgraded by one level for serious risk of bias related to a high risk of selective outcome reporting (see Assessment of risk of bias in included studies). We downgraded by one level for serious imprecision given the wide CIs of the point estimate of the treatment effect.

Potential biases in the review process

There is an earlier published version of this review (Bosteels 2010). Given our prior knowledge of potentially eligible studies for this clinical research topic, there might have been some potential for detection bias. We carried out a comprehensive literature search using a search strategy that was more extensive than the one used in the earlier published systematic review. This enabled us to identify a far greater number of randomised studies on hysteroscopic surgery in subfertile women, many of which did not address the particular research questions prespecified in the protocol (see Characteristics of excluded studies table).

Agreements and disagreements with other studies or reviews

According to one systematic review and critical appraisal, robust and high-quality RCTs are needed before hysteroscopy can be regarded as a first-line procedure in all infertile women, especially during the basal clinical assessment of the couple, when assisted reproductive treatment is not indicated yet (Di Spiezio Sardo 2016).

The findings and conclusions on the evidence for the removal of fibroids by hysteroscopy are in accordance with the findings of one Cochrane Review (Metwally 2012). The authors concluded that there was currently no definitive evidence from RCTs regarding the effect of hysteroscopic myomectomy on fertility outcomes. In contrast, according to the findings and conclusions of two systematic reviews of observational studies on fibroids and subfertility, fertility outcomes are decreased in women with submucosal fibroids, and removal is likely to benefit the reproductive outcome (Pritts 2001; Pritts 2009).

One Cochrane Review concluded that additional well-designed RCTs on the effectiveness of hysteroscopic polypectomy for improving reproductive outcome in subfertile women are needed, which is in accordance with our findings (Jayaprakasan 2014). One systematic review of mainly very-low quality observational studies concluded that polypectomy appeared to have a favourable outcome in infertile women (Lieng 2010b). Nevertheless, the body of evidence supporting the removal of endometrial polyps is limited, and future research evaluating the outcome of this common procedure is required.

One Cochrane Review concluded that there was no evidence to support hysteroscopic septum resection in women of reproductive age with a septate uterus to improve reproductive outcomes, although this procedure is often performed worldwide for this indication (Rikken 2017). RCTs are urgently needed (Rikken 2016): two studies are ongoing (SEPTUM trial; TRUST trial).

AUTHORS' CONCLUSIONS

Implications for practice

In women with otherwise unexplained subfertility and submucous fibroids, we are uncertain whether clinical pregnancy rates improved after hysteroscopic myomectomy compared to expectant management because there was only one small single-centre study of very low quality.

Hysteroscopic polypectomy may improve the chance of conceiving compared to diagnostic hysteroscopy only in subfertile women with a sonographic diagnosis of endometrial polyps prior to intrauterine insemination (IUI) for unexplained, male or female factor infertility for at least 24 months. The quality of the single-centre study retrieved was low.

Implications for research

The evidence retrieved from only two randomised studies was insufficient to address all the objectives of the present Cochrane Review.

More well-designed randomised controlled trials are needed to assess whether the hysteroscopic removal of endometrial polyps, submucous fibroids, septa or intrauterine adhesions is likely to benefit women with otherwise unexplained subfertility associated with these suspected uterine pathologies compared to a control intervention. Equally, more clinical research is needed on the effectiveness of treating endometrial polyps, submucous fibroids, septa or intrauterine adhesions in subfertile women bound to undergo IUI, in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI).

There are knowledge gaps concerning the effects of the number, size or extent and the localisation of the major uterine cavity abnormalities on the main outcomes in women with otherwise unexplained subfertility or prior to medically assisted reproduction.

Well-designed randomised studies are needed to assess the relationship between the timing of the hysteroscopic intervention and subsequent IUI, IVF or ICSI treatment.

Future randomised studies should report on primary outcomes such as live birth and adverse events such as miscarriage and hysteroscopic complications.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Casini 2006

Methods	<p>Parallel-group, randomised, controlled, single-centre trial</p> <p>Power calculation not reported</p> <p>Approved by the hospital's ethics committee</p> <p>No source of funding or conflict of interest reported</p>
Participants	<p>Country: Italy</p> <p>Setting: AGUNCO Obstetrics and Gynecology Centre, Rome</p> <p>Population: women referred to the centre from January 1998 to April 2005 for fertility problems were examined for inclusion. All women underwent routine examinations including the study of ovarian function (FSH, luteinising hormone, oestradiol and progesterone concentrations); prolactin, free triiodothyronine, free thyroxine and thyroid-stimulating hormone concentrations; postcoital test; TVUS; HSG and analysis of the partner's semen. The TVUS was performed to diagnose the presence of uterine fibroids. After these examinations, all women found to be affected by uterine fibroids excluding all other causes of infertility were asked to participate in the study</p> <p>Type of subfertility: infertility for ≥ 1 year (range: 1 to 5 years); no further clarification on primary versus secondary subfertility</p> <p>Mean age: women with submucous fibroids alone: 31.4 ± 2.5 years; women with mixed submucous-intramural fibroids: 32.2 ± 2.5 years</p> <p>Number recruited: 193 women</p> <p>Number participants: 181 women</p> <p>Number participants with submucous fibroids only: 52 women</p> <p>Number participants with mixed submucous-intramural fibroids: 42 women</p> <p>Inclusion criteria: aged ≤ 35 years; infertility for ≥ 1 year; presence of 1 knot or fibroid of diameter ≤ 40 mm (or both) and absence of other causes of infertility at the performed examinations</p> <p>Exclusion criteria: presence of ≥ 2 knots or fibroids of diameter > 40 mm (or both); body weight $> 20\%$ of normal weight; and use of medication containing oestrogens, progestins or androgens within 8 weeks prior to study</p> <p>Duration of study: 86 months; conducted January 1998 to April 2005</p>
Interventions	<ul style="list-style-type: none"> • Intervention group: hysteroscopic surgery to remove fibroids (52 women) • Control group: not treated (42 women) <p>Participants were examined by TVUS 3 months after surgery.</p> <p>Participants who underwent surgery were suggested to abstain from having sexual intercourse for 3 months and then to start having regular fertility-oriented intercourse. Participants who did not undergo surgery were asked to immediately start having regular fertility-oriented intercourse (intercourse during the 6-day fertile interval ending on the day of ovulation)</p> <p>Participants were monitored for up to 12 months after study commencement</p>
Outcomes	<p>Clinical pregnancy defined by the visualisation of an embryo with cardiac activity at 6-7 weeks of pregnancy</p> <p>Miscarriage classified as clinical loss of an intrauterine pregnancy between the 7th and</p>

	12th weeks of gestation	
Notes	<p>Authors stated that the differences in pregnancy rates between the comparison groups were statistically significant for the women with submucous fibroids ($P < 0.05$), which is in contrast with the calculation of the results in Review Manager 5</p> <p>The definition of knot was unclear: it could not be clarified since we were unable to contact the study authors</p> <p>Unclear whether a hysteroscopy was done in all women to confirm the exact position of the ultrasonically detected fibroids</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "Subsequently, women of each group were randomized into two sub-groups, according to a randomisation table."</p> <p>Comment: low risk of selection bias related to random sequence generation</p>
Allocation concealment (selection bias)	Unclear risk	<p>Method not stated: no further clarification obtained from the study authors</p> <p>Comment: unclear risk of selection bias related to allocation concealment</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Method not stated: no further clarification obtained from the study authors</p> <p>Comment: not applicable as this is a surgical study with unequivocal outcomes</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Method not stated: no further clarification obtained from the study authors</p> <p>Comment: not applicable as this is a surgical study with unequivocal outcomes</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Quote: "One hundred and ninety-three patients were diagnosed as affected by uterine fibroid excluding all other causes of infertility and met the requirements of the inclusion and exclusion criteria. Of these, 181 decided to participate in the study. Among the 181 patients, 52 had submucosal fibroids (SM group) while 45 had intramural fibroids (IM group), 11 had subserosal fibroids (SS group), 42 had a mix of submucosal-intramural (SM-IM group) and 31 patients had a mix of intramural-subserosal</p>

Casini 2006 (Continued)

		<p>fibroids (IM-SS group).” Quote: “Out of 181 women, 68 become pregnant.” Comment: low risk for attrition bias.</p>
Selective reporting (reporting bias)	High risk	All specified outcomes reported in the results section. Nevertheless, the published report failed to include results for the live birth rate, which was the primary outcome of interest that would be expected to have been reported for a trial on fertility treatment conducted over a 7-year period
Other bias	Unclear risk	<p>The mean ages and duration of infertility in the intervention and control group of women with submucous fibroids were not reported. No further clarification by the authors was obtained</p> <p>It was unclear whether there might have been imbalance in the baseline characteristics between the comparison groups</p> <p>Failure to do a hysteroscopy in all women to confirm the position of the ultrasonically detected fibroids could have caused information bias</p>

Pérez-Medina 2005

Methods	<p>Parallel-group, randomised, controlled, single-centre trial</p> <p>Power analysis performed. To detect an expected difference in pregnancy rate between the intervention and control group of 15% at a level of 0.05 with a power of 80%, a sample size of 200 women (i.e. 100 women per group) was required. From 2800 women attending the centre, 452 women fulfilling the inclusion criteria were selected; 215 women were randomised (107 women in the intervention group and 108 women in the control group). Data on outcomes of 204 women were available for analysis (101 in the intervention group and 103 in the control group). This study had therefore adequate statistical power to detect a difference between the comparison groups if really present</p> <p>Approved by the hospital’s ethics committee.</p> <p>No source of funding or conflict of interest reported.</p>
Participants	<p>Country: Spain</p> <p>Setting: infertility unit of an university tertiary hospital in the Spanish capital Madrid</p> <p>Population: women with unexplains, male or female factor infertility for ≥ 24 months bound to undergo IUI with a sonographic diagnosis of endometrial polyps</p> <p>Unexplained infertility was diagnosed in women with normal ovulatory cycles, semen analysis, HSG and postcoital testing. Male factor infertility was diagnosed if 2 semen analyses obtained ≥ 1 month apart were subnormal according to the WHO criteria. Female factor infertility was diagnosed in women with ovulatory dysfunction, cervical factor or endometriosis</p>

	<p>Type of subfertility: primary subfertility (correspondence with study authors) Mean age: treatment group: 30.8 years (range 26.7 to 34.9); control group: 30.9 years (range 26.5 to 35.3) Number recruited: 452 women Number randomised: 215 women Inclusion criteria: women with ≥ 24 months of subfertility with a sonographic diagnosis of endometrial polyps bound to undergo IUI for unexplained, male or female factor infertility Exclusion criteria: women aged > 39 years, anovulation, azoospermia, uncorrected tubal disease or previous unsuccessful use of recombinant FSH Duration of the study: 50 months; conducted January 2000 to February 2004</p>
<p>Interventions</p>	<p>1 surgeon (the first author of the study) performed all hysteroscopic procedures by intention in an outpatient clinic setting under local anaesthesia</p> <ul style="list-style-type: none"> • Hysteroscopic polypectomy using a 5.5 mm continuous flow office hysteroscope with a 1.5 mm scissors and forceps (107 women) • Diagnostic hysteroscopy using a 5.5 mm continuous flow office hysteroscope and polyp biopsy (108 women) <p>Duration: women were scheduled to receive 4 cycles of IUI with subcutaneous injection of recombinant FSH 50 IU daily from the 3rd day, and the first IUI was planned for 3 cycles after hysteroscopy in both groups. 4 IUI cycles were attempted before finishing the trial</p>
<p>Outcomes</p>	<p>Primary: quote: “We studied the crude pregnancy rate in both groups” Comment: clinical pregnancy; crude pregnancy was defined by the study authors as follows: “the presence of a gestational sac on ultrasound” (correspondence with the study authors) Secondary: time-to-pregnancy and influence of the size of the endometrial polyps on the pregnancy rate</p>
<p>Notes</p>	<p>All study data were obtained in personal communication from the study authors</p> <p>1. Quote: “Patients underwent a complete infertility evaluation that included TVUS in the early proliferative phase, basal body temperature recording to assess ovulation, postcoital test (PCT), HSG, semen analysis and, in some patients, diagnostic laparoscopy.”</p> <p>Comment: according to correspondence with the first author, the aim of the laparoscopy was exclusively diagnostic in the evaluation of cases of unexplained infertility of unknown origin. If tubal pathology was detected by laparoscopy, the participant was excluded from randomisation. The numbers of women undergoing a laparoscopy were balanced between the 2 comparison groups</p> <p>2. This study performed IUI for various indications: male factor (21%), cervical factor (11%), endometriosis (11%), or unexplained subfertility (49%) and ovulation disorder (33%). Anovulation was reported in the methods section as an exclusion criterion. The study authors defined ovulation disorder as follows: quote: “A combination of irregular menstrual cycles with multicystic ovaries on TVUS and basal gonadotrophin measurements within the normal range” (correspondence with the first study author). Comment: in everyday clinical practice ovulation disorder is not an indication for IUI by itself</p> <p>3. Data on the number or the localisation of the polyps could not be retrieved since the first author no longer works in the university hospital</p>

	4. Data on the size of the polyps in the control group could not be obtained for similar reasons as note 3	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomised to one of the two groups with use of an opaque envelope technique, with assignment determined by a computerized random number table." Quote: "Subjects were randomised into one of two groups in a 1:1 ratio using a restricted randomisation." Comment: probably done, but using simple randomisation, with an equal allocation ratio, by referring to a table of random numbers generated by a computer
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomised to one of the two groups with use of an opaque envelope technique, with assignment determined by a computerized random number table." Comment: sequentially numbered, opaque, sealed envelopes were used according to correspondence with the first author; probably done
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Method not stated: no further clarification obtained from the study authors Comment: not applicable as this is a surgical study with unequivocal outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Method not stated: no further clarification obtained from the study authors Comment: not applicable as this is a surgical study with unequivocal outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "11 patients were lost from the study, 6 in the study group (3 lost to follow-up, 2 pathologic reports of submucosal myoma and 1 in whom the polyp was not confirmed) and 5 in the control group (1 lost to follow-up, 2 in whom the polyp was not confirmed and 2 pathologic reports of myoma)." Comment: missing outcome data were bal-

		anced in numbers across the comparison groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	High risk	All specified outcomes reported in the results section. The final study report nevertheless failed to include results for the live birth rate, which is the primary outcome of interest expected for a trial on fertility treatment conducted over a 4-year period. Data on the outcomes live birth and miscarriage were not available since most the majority of randomised women were referred by gynaecologists from outside the tertiary university hospital and were referred back when pregnant for further follow-up by the referring gynaecologist. No clarification could be obtained for the lack of data on hysteroscopic complications
Other bias	Low risk	No evidence for imbalance in the baseline characteristics.

CI: confidence interval; FSH: follicle-stimulating hormone; HSG: hysterosalpingography; IU: international units; IUI: intrauterine insemination; TVUS: transvaginal ultrasound; WHO: World Health Organization.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Abiri 2014	Not addressing the research questions described in the protocol RCT in women with no suspected major uterine cavity abnormalities undergoing a first IVF treatment cycle
Abu Rafea 2013	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing intrauterine balloon stenting vs no stenting following hysteroscopic treatment for septate uterus
Acunzo 2003	Not addressing the research questions described in the protocol Parallel-group randomised trial studying the efficacy of hyaluronic acid gel in preventing the development of intrauterine adhesions following hysteroscopic adhesiolysis. Mixed population of women with intrauterine adhesions, presenting with subfertility or other gynaecological complaints. Primary outcome: adhesion scores

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Aghahosseini 2012	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing hysteroscopy prior to a subsequent IVF attempt vs immediate IVF without prior hysteroscopy conducted in women with ≥ 2 failed IVF cycles with unsuspected or no uterine cavity abnormalities. Main outcomes: biochemical pregnancy, clinical pregnancy and delivery rates
Aghajanova 2018	Not addressing the research questions described in the protocol Randomised controlled open pilot clinical trial studying the efficacy of the intrauterine infusion of autologous platelet rich plasma vs saline infusion after operative hysteroscopy for the management of moderate-to-severe Asherman's syndrome
Aleyassin 2017	Not addressing the research questions described in the protocol RCT studying the effectiveness of routine hysteroscopy compared to no prior hysteroscopy in women with normal transvaginal ultrasound and HSG before the first ICSI treatment cycle
Amer 2010	Not addressing the research questions described in the protocol Parallel-group randomised trial in subfertile women comparing the application of amnion graft, either fresh or dried to an intrauterine balloon vs the application of an intrauterine balloon without amnion graft as an adjunctive procedure after the hysteroscopic lysis of severe intrauterine adhesions, diagnosed at clinic hysteroscopy in women with infertility with or without menstrual disorders as the primary symptom. Outcomes: improvement in adhesion grade, improvement in menstruation, increased uterine length at sounding, complications and reproductive outcome
Basma 2013	Not addressing the research questions described in the protocol Women with detectable uterine pathology by ultrasound were excluded from participating in the trial aiming to study the effectiveness of hysteroscopy before a first trial ICSI
Cao 2018	Not addressing the research questions described in the protocol Systematic review including clinical trials of hysteroscopy with or without endometrial biopsy in women with recurrent implantation failure and no suspected intrauterine lesions
Chen 2017	Not addressing the research questions described in the protocol RCT investigating the effects of mindfulness-based stress reduction on anxiety, depression and quality of life in women with intrauterine adhesions
Clark 2015	Not addressing the research questions described in the protocol The target population included women with abnormal uterine bleeding and hysteroscopically diagnosed uterine polyps
Colacurci 2007	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing 2 different surgical techniques for metroplasty: operative hysteroscopy using the resectoscope with a unipolar knife vs the Versapoint device. Mixed population of women with septate uterus and a history of recurrent miscarriage or primary subfertility. Outcomes: operative parameters, complications, need for a second intervention and reproductive outcome parameters
Darwish 2009	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing extended sectioning by resectoscopy vs sequential cold knife excision for treating a complete utero-cervicovaginal septum in a mixed population of women with infertility or pregnancy loss. Main outcomes: operating time, perioperative bleeding, complications, reproductive

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	outcome, and participant and husband satisfaction
De Angelis 2010	Study on the effectiveness of hysteroscopic metroplasty for small septate uterus in women with repeated IVF implantation failure. Although denoted by the authors as the first prospective randomised controlled study on this subject, the trial did not use a valid random sequence generation Quote: "These patients, once informed about the situation, were randomly allocated, depending on their personal decision ..."
De Iaco 2003	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing the application of hyaluronan derivative gel (Hyalobarrier gel) after hysteroscopic surgery vs surgical treatment alone in women aged 18-65 years, with gynaecological conditions other than subfertility. Primary outcome: adhesion score at second-look hysteroscopy
Demiroglu 2004	Not addressing the research questions described in the protocol Parallel-group randomised comparison between clinic hysteroscopy prior to a subsequent IVF attempt or immediate IVF without prior clinic hysteroscopy conducted in women with ≥ 2 failed IVF cycles with unsuspected or no uterine cavity abnormalities. Outcomes: number of oocytes retrieved, fertilisation rate, number of embryos transferred, first trimester miscarriage and clinical pregnancy rates
Di Florio 2013	Not addressing the research questions described in the protocol RCT comparing the new 16 Fr mini-resectoscope with the traditional 22 Fr resectoscope and Bettocchi 15 Fr hysteroscope for the treatment of uterine cavity lesions
Di Spiezio Sardo 2011	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing the use of Intercoat absorbable adhesion barrier gel vs no adhesion barrier after hysteroscopic synechiolysis in a mixed population of women with infertility or other gynaecological conditions. Primary outcomes: incidence of de novo intrauterine adhesions, adhesion scores and patency of the internal uterine ostium
El-Khayat 2015	Not addressing the research questions described in the protocol RCT evaluating the role of endometrial injury in the cycle preceding ovarian stimulation for IUI cycle on the clinical pregnancy rate
El-Nashar 2011	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing diagnostic hysteroscopy with directed biopsy or hysteroscopic treatment of unsuspected uterine cavity abnormalities (or both) vs no hysteroscopy in women with primary infertility treated with ICSI. Primary outcome: clinical pregnancy
El-Toukhy 2009	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing hysteroscopy vs no hysteroscopy in women with recurrent implantation failure with IVF. Status: completed
Elsetohy 2015	Not addressing the research questions described in the protocol Parallel-group randomised trial aimed at assessing the role of using clinic hysteroscopy as a routine investigation in improving ICSI pregnancy rates in 2 groups of infertile women with no abnormality detected on transvaginal ultrasonographic examination
Fatemi 2007	Not addressing the PICO research question of this Cochrane Review

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Fuchs 2014	Not addressing the PICO research question of this Cochrane review RCT evaluating the safety and effectiveness of Oxiplex/AP gel (Intercoat) in reducing intrauterine adhesion formation after hysteroscopic treatment because of retained products of conception
Gan 2017	Not addressing the PICO research question of this Cochrane Review RCT studying the efficacy of freeze-dried amnion graft for prevention of intrauterine adhesion reformation after hysteroscopic adhesiolysis
Gao 2013	Observational non-randomised study on the effectiveness of hysteroscopy in women with repeated implantation failure
Guida 2004	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing hysteroscopic surgery for the removal of polyps, fibroids or septa followed by the application of auto-cross linked hyaluronic acid gel vs hysteroscopic surgery without the adhesion barrier in a mixed population of women with subfertility and other gynaecological symptoms associated with endometrial polyps, submucous fibroids or septa. Main outcomes: rates of adhesion formation and adhesion scores
Guo 2017	Not addressing the research questions described in the protocol Prospective, randomised, controlled trial to evaluate the efficacy of different doses of oestrogen treatment (2 mg and 6 mg daily) after hysteroscopic adhesiolysis in women with moderate-to-severe adhesion according to the American Fertility Society classification of intrauterine adhesions
Hamerlynck 2015	Not addressing the research questions described in the protocol Multicentre, open-label, randomised, controlled trial comparing hysteroscopic morcellation with bipolar resectoscopy for removal of endometrial polyps, in terms of procedure time, peri- and postoperative adverse events, tissue availability and short-term effectiveness
Hanstede 2016	Not addressing the research questions described in the protocol Single-blind RCT assessing whether exogenous hormone administration starting immediately after a successful hysteroscopic adhesiolysis, in women with Asherman's syndrome may reduce the incidence of spontaneous recurrence of adhesions more than the endogenous production of hormones
Hare 2013	Not addressing the research questions described in the protocol Randomised controlled study examining the effect of scratching in a normal visually and histologically endometrium. Women with uterine pathology were excluded before or during clinic hysteroscopy
Javidan 2017	Not addressing the research questions described in the protocol Single-blind RCT to assess the outcomes of surgery in a group of women who were randomly submitted to preoperative gonadotropin-releasing hormone agonists in comparison with women who received no medication
Kamel 2014	Not addressing the research questions described in the protocol Randomised controlled study to compare mechanical (cold scissor) vs electrosurgical metroplasty (bipolar twizzle) in terms of feasibility and pain scoring during ambulatory-based hysteroscopic metroplasty for short, narrow-based uterine septa

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Lara-Dominguez 2016	Not addressing the research questions described in the protocol RCT comparing the resection of endometrial polyps with 2 different devices: the Versapoint bipolar electrode and the diode laser
Lieng 2010a	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing transcervical resection by hysteroscopy of endometrial polyps suspected on TVUS and SIS vs observation for 6 months. The study population included premenopausal women with bleeding problems associated with endometrial polyps. The aim of the trial was to study the clinical effectiveness of transcervical resection of endometrial polyps for the outcome periodic blood loss. Women wishing to become pregnant were excluded from the trial. Primary outcome: periodic blood loss measured by the Pictorial Blood Assessment Chart
Lin 2014	Not addressing the research questions described in the protocol Randomised trial comparing the efficacy of intrauterine balloon and intrauterine contraceptive device in the prevention of adhesion reformation following hysteroscopic adhesiolysis
Liu 2016	Not addressing the research questions described in the protocol RCT randomly comparing oestradiol valerate (Progynova) 3 mg or 9 mg per diet before surgery or no hormonal treatment before transcervical resection of adhesions
Mohammed 2014	Comparative non-randomised study on the value of hysteroscopy prior to IVF/ICSI
Moramezi 2012	Not addressing the research questions described in the protocol RCT studying the effectiveness of hysteroscopy before IUI on reproductive outcome in infertile women with no suspected intrauterine lesions during baseline fertility assessment
Muzii 2007	Not addressing the research questions described in the protocol Parallel-group randomised trial in women aged 18-75 years comparing operative hysteroscopy using the monopolar resectoscope vs hysteroscopic bipolar electrode excision for the treatment of endometrial polyps. Outcomes: operating times, difficulty of the operation, surgeon satisfaction with the procedure, complications, postoperative pain and participant satisfaction
Muzii 2017	Not addressing the research questions described in the protocol Multicentric randomised trial in 180 women affected by endometrial hyperplasia, myomas or endometrial polyps undergoing operative hysteroscopy comparing cefazolin 2 g intravenously 30 minutes prior to the procedure vs no antibiotic treatment
Nappi 2013	Not addressing the research questions described in the protocol Double-blind, randomised, placebo-controlled study to assess the incidence of infectious complications and the protective effect of antibiotic administration during operative hysteroscopic procedures in a clinic setting. 1046 consecutively enrolled women with intrauterine lesions were randomly allocated to the intervention group (523 participants administered cefazolin 1 g intramuscularly) and the control group (523 participants administered with 10 mL of isotonic sodium chloride solution), and treated in clinic setting by operative hysteroscopy for endometrial polypectomy, uterine septa, submucosal myomas and intrauterine adhesions
Pabuccu 2008	Quasi-randomised trial comparing early second-look clinic hysteroscopic adhesiolysis after hysteroscopic adhesiolysis and IUD insertion vs no early second-look operative hysteroscopy in subfertile women with intrauterine adhesions. The method of sequence generation was based on alternation: women were allocated

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	to the intervention or control groups based on their study entry. Main outcomes: pregnancy and live birth rate
Parsanezhad 2006	Not addressing the research questions described in the protocol Parallel-group randomised trial in a mixed study population of women with a history of pregnancy wastage or infertility and an associated complete uterine septum comparing metroplasty with complete section of the cervical septum vs metroplasty with preservation of the cervical septum. Outcomes: operating time, distending media deficit, total distending media used, intraoperative bleeding, complications and reproductive outcome
Paz 2014	Not addressing the research questions described in the protocol Randomised, double-blind, controlled trial to evaluate the efficacy and safety of Intercoat (Oxiplex/AP Gel) in preventing intrauterine adhesions after operative hysteroscopy
Rama Raju 2006	Not addressing the research questions described in the protocol Parallel-group randomised trial conducted in women with ≥ 2 failed IVF cycles with unsuspected or no uterine cavity abnormalities comparing clinic hysteroscopy prior to a subsequent IVF attempt or immediate IVF without prior hysteroscopy. Outcomes: number of oocytes retrieved, fertilisation rate, number of embryos transferred and clinical pregnancy rates
Revel 2011	Not addressing the research questions described in the protocol Parallel-group RCT assessing the safety of hyaluronic acid gel to prevent intrauterine adhesions in hysteroscopic surgery
Roy 2014	Not addressing the research questions described in the protocol RCT to evaluate the efficacy of oestrogen in preventing intrauterine adhesions following hysteroscopic septal resection and to investigate its effect on reproductive outcome
Roy 2015	Not addressing the research questions described in the protocol RCT to compare the operation and reproductive outcome of hysteroscopic septal resection using unipolar resectoscope vs bipolar resectoscope
Roy 2017	Not addressing the research questions described in the protocol Randomised, prospective, parallel, comparative, single-blinded study comparing the operative and reproductive outcome of hysteroscopic myomectomy using unipolar resectoscope vs bipolar resectoscope in women with infertility and menorrhagia
Rubino 2015	Not addressing the research questions described in the protocol Randomised, prospective, comparative setting clinical trial to examine efficacy of hysteroscopic removal of polyps and myomas on health-related quality of life and symptom severity at 1-year postprocedure in a clinic vs ambulatory surgical centre
Shawki 2012	Not addressing the research questions described in the protocol Parallel-group randomised trial conducted to determine the incidence of unsuspected uterine cavity abnormalities detected by clinic hysteroscopy in women before ICSI treatment compared to ICSI without prior hysteroscopy. Main outcomes: incidence of unsuspected uterine abnormalities, and implantation and clinical pregnancy rates

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Shokeir 2010	Published report describing a parallel-group randomised trial comparing hysteroscopic myomectomy vs diagnostic hysteroscopy and biopsy in women with otherwise unexplained primary infertility and submucous fibroids. Primary outcome: clinical pregnancy rates Quote from <i>Fertility and Sterility</i> searched on 16 January 2012: “This article has been retracted at the request of the editor as it duplicates parts of a paper that had already appeared in <i>Hum. Reprod.</i> , 20 (2005) 1632-1635, DOI:10.1093/humrep/deh822.”
Smit 2015	Not addressing the research questions described in the protocol RCT assessing the interobserver agreement among gynaecologists who were randomised into 2 groups: 1 group received diagnostic criteria for a septate uterus before assessment of videos, whereas the other group assessed the recordings without instruction
Smit 2016	Not addressing the research questions described in the protocol Pragmatic, multicentre, RCT in women with a normal TVUS of the uterine cavity and no previous hysteroscopy who were scheduled for their first IVF treatment randomly comparing treatment with hysteroscopy of detected intracavitary abnormalities before starting IVF vs immediate start of the IVF treatment
Smith 2014	Not addressing the research questions described in the protocol Multicentre, single-blind, randomised, controlled trial to evaluate whether hysteroscopic morcellation or bipolar electrosurgical resection was more favourable for removing endometrial polyps in a clinic setting in terms of feasibility, speed, pain and acceptability
Sohrabvand 2012	Not addressing the research questions described in the protocol Parallel-group RCT to assess the effectiveness of diagnostic hysteroscopy in women prior to IVF/IICSI. The study population included women with a normal hysterosonography and normal vaginal ultrasound during the past 12 months
Tonguc 2010	Not addressing the research questions described in the protocol Parallel-group randomised study comparing hysteroscopic lysis of intrauterine adhesions with or without adjunctive therapy (cyclical hormone replacement therapy alone or intrauterine device alone or both cotreatments combined) after hysteroscopic metroplasty in a mixed population of women with subfertility or recurrent miscarriage (or both). Main outcomes: incidence of de novo adhesion formation and ongoing pregnancy rate
Trninić -Pjević 2011	Clinical controlled trial on the effectiveness of hysteroscopy prior to IVF; no random sequence generation
van Dongen 2008	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing the hysteroscopic removal of polyps or fibroids by conventional hysteroscopy using a resectoscope vs hysteroscopic morcellation in a mixed population of women with infertility or other gynaecological conditions. Outcomes: mean number of insertions into the uterine cavity and mean operating time
Vercellini 1993	Not addressing the research questions described in the protocol Parallel-group randomised comparing metroplasty using the resectoscope vs microscissors for treating uterine septum in women with repeated miscarriage. Outcomes: mean operating time, mean amount of distension medium used and complications

(Continued)

Weiss 2005	Not addressing the research questions described in the protocol Parallel-group RCT to determine whether performing curettage the month prior to embryo transfer increases the chance of embryo implantation
Xiao 2015	Not addressing the research questions described in the protocol Prospective, randomised, double-blind, controlled clinical trial assessing the efficacy and safety of auto-crosslinked hyaluronic acid gel for preventing intrauterine adhesions after hysteroscopic adhesiolysis
Youssef 2013	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing 2 different surgical techniques for metroplasty: resectoscopy with monopolar knife vs small-diameter hysteroscopy fitted with a 5 Fr reusable bipolar electrode. Outcomes: pregnancy, miscarriage and live birth rates

HSG: hysterosalpingography; ICSI: intracytoplasmic sperm injection; IUD: intrauterine device; IUI: intrauterine insemination; IVF: in vitro fertilisation; PICO: Participants, Interventions, Comparisons and Outcomes; RCT: randomised controlled trial; SIS: saline infusion sonography; TVUS: transvaginal ultrasound.

Characteristics of ongoing studies [ordered by study ID]

SEPTUM trial

Trial name or title	Assessment of hysteroscopic metroplasty in women with a uterine septum and a history of miscarriage: a randomised controlled trial - SEPTUM
Methods	Pilot multicentre randomised controlled trial to assess feasibility for a larger adequately powered trial
Participants	Women with septate uteri, history of miscarriage or preterm birth, or infertility
Interventions	Intervention: hysteroscopic septal resection Comparator: no intervention
Outcomes	Primary outcome ● Live birth surviving until discharge from hospital Secondary outcomes ● Uterine perforation ● Fluid overload ● Endometritis ● Bleeding ● Incomplete resection ● Synechiae or adhesions ● Clinical pregnancy rate ● Miscarriage (first or second trimester) ● Premature delivery (< 34 weeks and < 37 weeks) ● Ectopic pregnancy ● Uterine rupture

SEPTUM trial (Continued)

	<ul style="list-style-type: none"> • Delivery (vaginal, elective or emergency) • Postpartum haemorrhage (1500 mL) • Placenta praevia • Morbidly adherent placenta
Starting date	9 December 2014
Contact information	Dr Matthew Prior Subspecialty Registrar in Reproductive Medicine and Surgery Newcastle Fertility Centre email: matt@matthewprior.com mobile: +44 7817 627 712
Notes	Quote: “The trial is ongoing but closed to recruitment due to feasibility issues with recruitment. Six participants were recruited and will be followed up for 24 months post intervention.”

TRUST trial

Trial name or title	TRUST - The Randomised Uterine Septum Transsection trial
Methods	Multicentre, parallel-group, randomised controlled trial. No masking/blinding
Participants	<p>Inclusion criteria</p> <ul style="list-style-type: none"> • Women with women with subfertility or preterm birth ≥ 2 preceding miscarriages before 20 weeks of gestational age and a septate uterus • Diagnosis of a septate uterus • Active wish to conceive. <p>Exclusion criteria</p> <ul style="list-style-type: none"> • Prior randomisation in the TRUST • Contraindications for surgery
Interventions	Intervention: hysteroscopic metroplasty Comparator: no surgical resection
Outcomes	<p>Primary outcome</p> <ul style="list-style-type: none"> • Live birth rate (defined as a live birth after 24 weeks of gestational age) <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Complications following hysteroscopic metroplasty • Obstetrical complications
Starting date	1 October 2008
Contact information	Dr JFW Rikken
Notes	4 May 2018: inclusion of 63rd participant; targeted sample size = 68 Trial website: www.studies-obsgyn.nl/trust/

DATA AND ANALYSES

Comparison 1. Operative hysteroscopy versus control in women with otherwise unexplained subfertility and suspected major uterine cavity abnormalities

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical pregnancy	1	94	Odds Ratio (M-H, Fixed, 95% CI)	2.44 [0.97, 6.17]
1.1 Removal of submucous fibroids only vs no surgery	1	52	Odds Ratio (M-H, Fixed, 95% CI)	2.04 [0.62, 6.66]
1.2 Removal of mixed submucous-intramural fibroids vs no surgery	1	42	Odds Ratio (M-H, Fixed, 95% CI)	3.24 [0.72, 14.57]
2 Adverse events: miscarriage	1	94	Odds Ratio (M-H, Fixed, 95% CI)	1.54 [0.47, 5.00]
2.1 Removal of submucous fibroids only vs no surgery	1	52	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.27, 5.97]
2.2 Removal of mixed submucous-intramural fibroids vs no surgery	1	42	Odds Ratio (M-H, Fixed, 95% CI)	2.0 [0.32, 12.33]

Comparison 2. Operative hysteroscopy versus control in women undergoing medically assisted reproduction with suspected major uterine cavity abnormalities

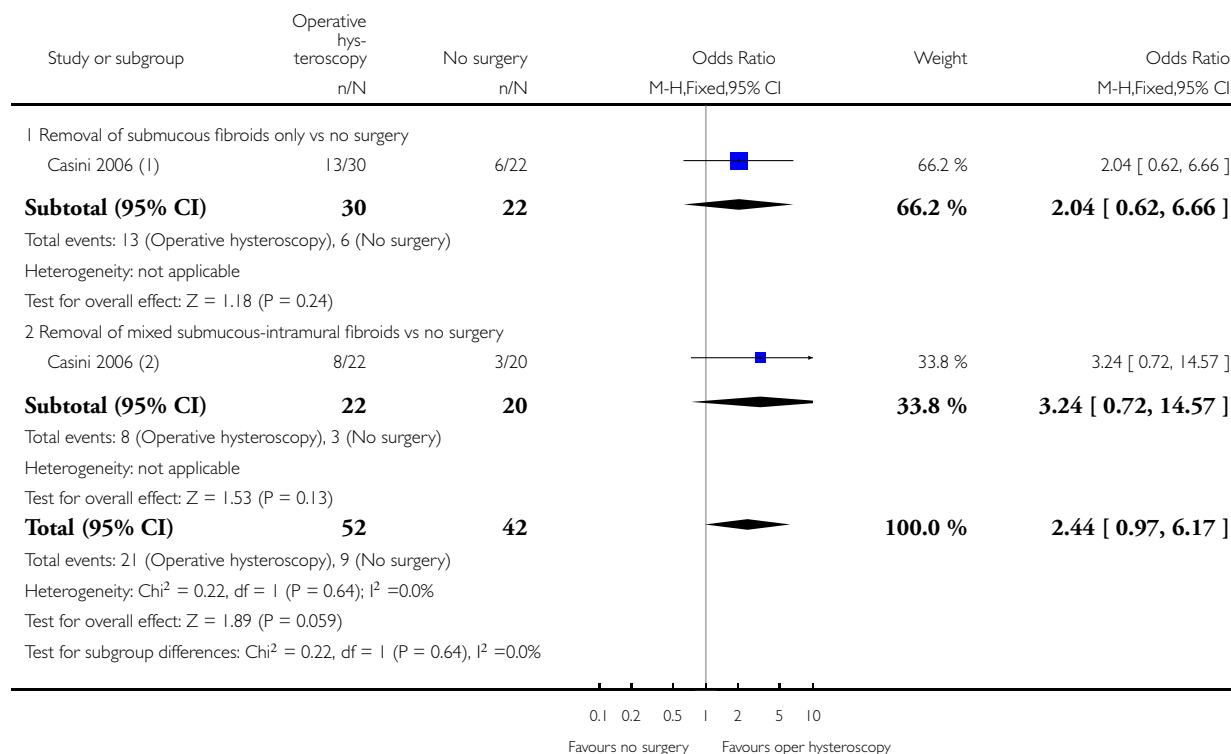
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical pregnancy	1	204	Odds Ratio (M-H, Fixed, 95% CI)	4.41 [2.45, 7.96]
1.1 Hysteroscopic polypectomy vs diagnostic hysteroscopy and biopsy only prior to intrauterine insemination	1	204	Odds Ratio (M-H, Fixed, 95% CI)	4.41 [2.45, 7.96]

Analysis 1.1. Comparison 1 Operative hysteroscopy versus control in women with otherwise unexplained subfertility and suspected major uterine cavity abnormalities, Outcome 1 Clinical pregnancy.

Review: Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities

Comparison: 1 Operative hysteroscopy versus control in women with otherwise unexplained subfertility and suspected major uterine cavity abnormalities

Outcome: 1 Clinical pregnancy



(1) The intervention was the hysteroscopic removal of fibroids. The comparison arm was no surgical removal of fibroids.

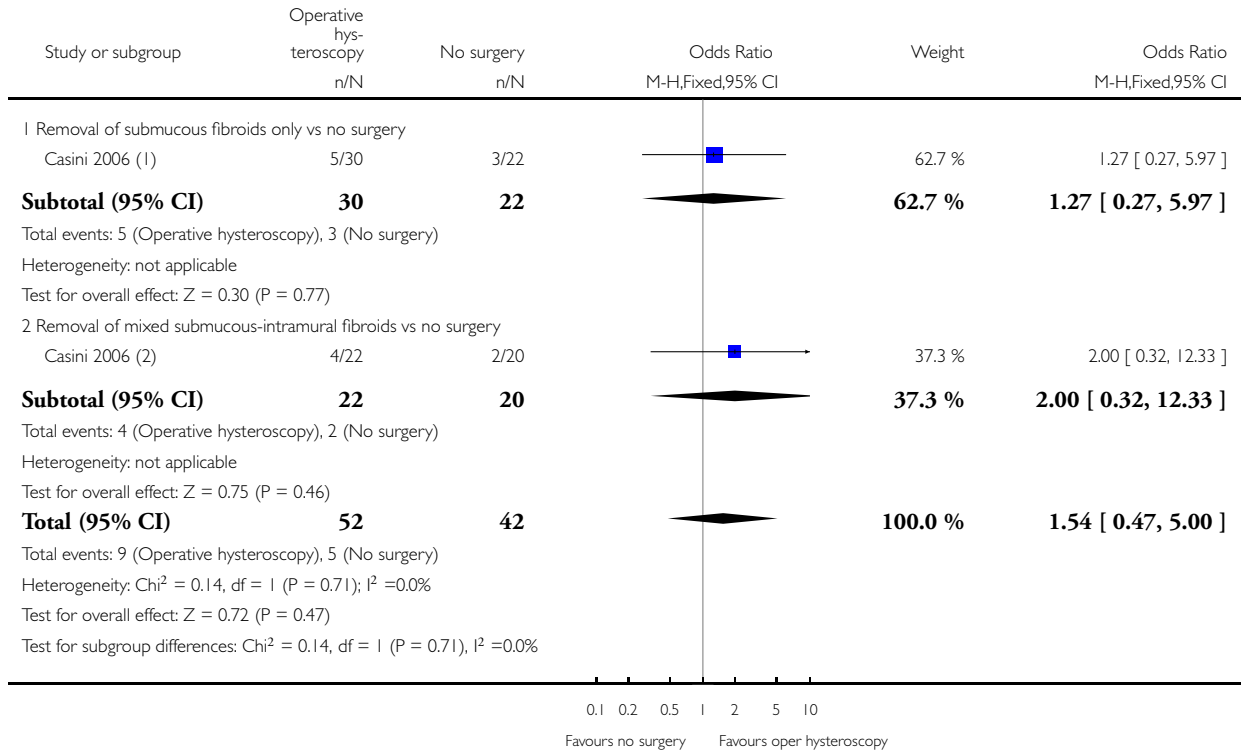
(2) The intervention was the hysteroscopic removal of fibroids. The comparison arm was no surgical removal of fibroids.

Analysis 1.2. Comparison 1 Operative hysteroscopy versus control in women with otherwise unexplained subfertility and suspected major uterine cavity abnormalities, Outcome 2 Adverse events: miscarriage.

Review: Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities

Comparison: 1 Operative hysteroscopy versus control in women with otherwise unexplained subfertility and suspected major uterine cavity abnormalities

Outcome: 2 Adverse events: miscarriage



(1) The intervention was the hysteroscopic removal of fibroids. The comparison arm was no surgical removal of fibroids.

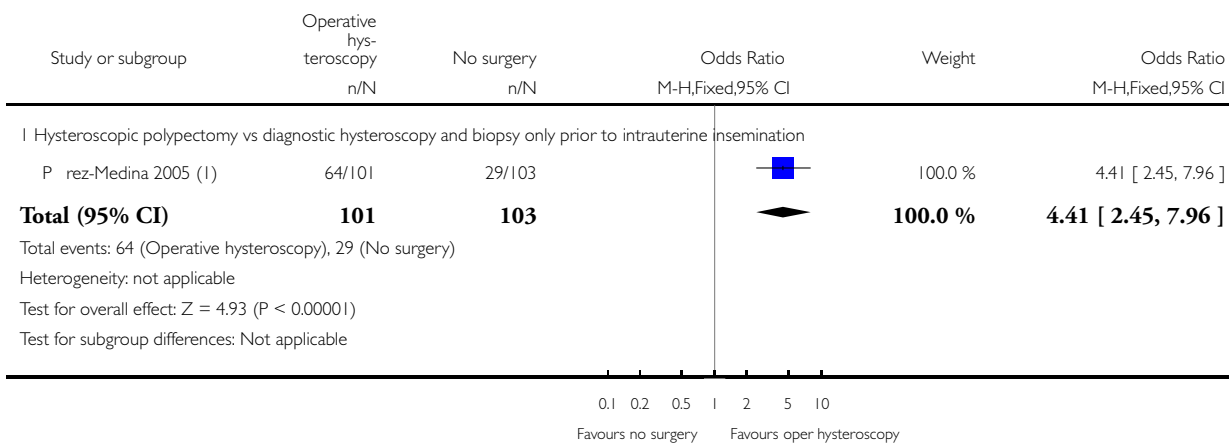
(2) The intervention was the hysteroscopic removal of fibroids. The comparison arm was no surgical removal of fibroids.

Analysis 2.1. Comparison 2 Operative hysteroscopy versus control in women undergoing medically assisted reproduction with suspected major uterine cavity abnormalities, Outcome 1 Clinical pregnancy.

Review: Hysteroscopy for treating subfertility associated with suspected major uterine cavity abnormalities

Comparison: 2 Operative hysteroscopy versus control in women undergoing medically assisted reproduction with suspected major uterine cavity abnormalities

Outcome: 1 Clinical pregnancy



(I) The intervention was the hysteroscopic removal of polyps. The comparison arm was simple diagnostic hysteroscopy with biopsy.

ADDITIONAL TABLES

Table 1. Effect of polyp size on clinical pregnancy rates in the intervention group

Polyp size	Clinical pregnancy ^a	Clinical pregnancy rate (95% CI) ^b
< 5 mm	19/25	76% (72% to 80%)
5-10 mm	18/32	56% (53% to 59%)
11-20 mm	16/26	61% (58% to 65%)
> 20 mm	11/18	61% (58% to 64%)

CI: confidence interval.

^aClinical pregnancy is defined by a pregnancy diagnosed by ultrasound visualisation of at least one gestational sac per woman randomised.

^bNo significant difference was found for the clinical pregnancy rates between the 4 subgroups ($P = 0.32$).

Table 2. GRADE evidence profile - unexplained subfertility and submucous fibroids

Quality assessment						
Submucous fibroids and unexplained subfertility						
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
Clinical pregnancy (follow-up 1 year; ultrasound ^a)						
1	RCT	Very serious ^b	Not serious	Not indirectness	Serious ^c	None
Miscarriage (follow-up 1 year; ultrasound ^d)						
1	RCT	Very serious ^b	Not serious	Not serious	Serious ^c	None

^aA clinical pregnancy was defined by the visualisation of an embryo with cardiac activity at six to seven weeks' gestational age.

^bUnclear allocation concealment and high risk of selective outcome reporting.

^cWide confidence intervals.

^dMiscarriage was defined by the clinical loss of an intrauterine pregnancy between the 7th and 12th weeks of gestation.

Table 3. GRADE evidence profile - endometrial polyps prior to intrauterine insemination

Quality assessment						
Endometrial polyps prior to gonadotropin and IUI treatment						
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations
Clinical pregnancy (follow-up 4 IUI cycles; ultrasound ^a)						
1	RCT	Serious ^b	Not serious	Not serious	Not serious	None

IUI: intrauterine insemination; RCT: randomised controlled trial.

^aClinical pregnancy was defined by the presence of at least one gestational sac on ultrasound.

^bThere was high risk for selective outcome reporting bias.

APPENDICES

Appendix 1. The Cochrane Gynaecology and Fertility Group (CGFG) specialised register search strategy

Searched 16 April 2018

PROCITE Platform

Keywords CONTAINS “hysteroscopic ” or “hysteroscopy” or “hysteroscope” or “endoscopy” or Title CONTAINS “hysteroscopic ” or “hysteroscopy” or “hysteroscope” or “endoscopy”

AND

Keywords CONTAINS “subfertility” or “subfertility-Female” or “infertility” or “IVF” or “ICSI” or “IUI” or “in vitro fertilisation” or “in vitro fertilization” or “Intrauterine Insemination” or “artificial insemination” or “assisted conception” or “assisted reproduction techniques” or “myoma” or “myomas” or “myomectomy” or “septate uterus” or “polypectomy” or “polyp removal” or “polyps” or “adhesiolysis” or “adhesion” or “adhesions” or “synechiotomy” or “Leiomyoma” or “leiomyomata” or “fibroids” or “Asherman’s Syndrome” or “uterine septa” or “uterine septum” or “uterine disease” or “uterine leiomyomas” or “uterine malformation” or “Uterine Neoplasms” or “uterine polyps” or “metroplasty” or “intrauterine adhesions” or “fibroid” or “fibroids” or Title CONTAINS “subfertility” or “assisted reproduction techniques” or “myoma” or “myomas” or “myomectomy” or “septate uterus” or “polypectomy” or “metroplasty” or “intrauterine adhesions” or “fibroid” or “fibroids”

272 records

Appendix 2. CENTRAL Register of Studies Online (CRSO) search strategy

Searched 16 April 2018

Web Platform

#1 MESH DESCRIPTOR Hysteroscopy EXPLODE ALL TREES 349

#2 Hysteroscop*:TI,AB,KY 902

#3 endoscop*:TI,AB,KY 17242

#4 #1 OR #2 OR #3 18070

#5 MESH DESCRIPTOR Infertility, Female EXPLODE ALL TREES 1127

#6 (subfertil* or infertil*):TI,AB,KY 5049

#7 MESH DESCRIPTOR Reproductive Techniques, Assisted EXPLODE ALL TREES 2919

#8 (IVF or ICSI):TI,AB,KY 4175

#9 (artificial insemination):TI,AB,KY 182

#10 (assisted conception):TI,AB,KY 86

#11 (in vitro fertili*):TI,AB,KY 2233

#12 (intracytoplasmic sperm):TI,AB,KY 1373

#13 (intrauterine insemination):TI,AB,KY 734

#14 MESH DESCRIPTOR Leiomyoma EXPLODE ALL TREES 449

#15 MESH DESCRIPTOR myoma EXPLODE ALL TREES 21

#16 (myoma* or myomectom*):TI,AB,KY 946

#17 Leiomyoma*:TI,AB,KY 631

#18 (sept* uter*):TI,AB,KY 19

#19 (?Uter* adj4 polyp*):TI,AB,KY 38

#20 (Endometri* adj4 polyp*):TI,AB,KY 172

#21 (adhesiolysis or septoplast* or metroplast*):TI,AB,KY 381

#22 MESH DESCRIPTOR Tissue Adhesions EXPLODE ALL TREES 342

#23 (remov* adj2 adhesion*):TI,AB,KY or (?intrauter* adj2 adhesion*):TI,AB,KY 62

#24 synech*:TI,AB,KY 270

#25 (uter* adj2 malform*):TI,AB,KY 38

#26 (Uter* adj4 Neoplasm*):TI,AB,KY 2161

#27 (uter* adj4 abnormalit*):TI,AB,KY 99

#28 fibroid*:TI,AB,KY 557

#29 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 12761
#30 #4 AND #29 623

Appendix 3. MEDLINE search strategy

Searched from 1946 to 16 April 2018

OVID Platform

- 1 exp Hysteroscopy/ (4330)
- 2 Hysteroscop\$.tw. (6123)
- 3 Uteroscop\$.tw. (13)
- 4 endoscop\$.tw. (179897)
- 5 Endoscopy/ (47569)
- 6 or/1-5 (201815)
- 7 exp Infertility/ (60956)
- 8 subfertil\$.tw. (4522)
- 9 Infertilit\$.tw. (44291)
- 10 exp Sperm Injections, Intracytoplasmic/ or exp Reproductive Techniques/ or exp Reproductive Techniques, Assisted/ or exp Fertilization in Vitro/ (137421)
- 11 (in vitro fertili\$ or intracytoplasmic sperm).tw. (25251)
- 12 (IVF or ICSI).tw. (24282)
- 13 IUI.tw. (1544)
- 14 artificial insemination.tw. (5969)
- 15 (intrauter* adj2 inseminat*).tw. (2287)
- 16 assisted conception.tw. (1110)
- 17 assisted reproduct*.tw. (12595)
- 18 exp Myoma/ or exp Leiomyoma/ (21709)
- 19 (myoma or myomectomy).tw. (5800)
- 20 septoplast*.tw. (1522)
- 21 Asherman* syndrome.tw. (251)
- 22 metroplast*.tw. (363)
- 23 (sept* adj2 resect*).tw. (382)
- 24 septate uterus.tw. (392)
- 25 polypectomy.tw. (4158)
- 26 (remov\$ adj2 polyp*).tw. (1326)
- 27 adhesiolysis.tw. (1346)
- 28 exp Tissue Adhesions/ (11844)
- 29 (?intrauter* adj2 adhesion\$).tw. (445)
- 30 (remov\$ adj4 adhesion\$).tw. (414)
- 31 polyp\$.tw. (254390)
- 32 uterine septa.tw. (92)
- 33 uterine septum.tw. (231)
- 34 synech*.tw. (9278)
- 35 Leiomyoma\$.tw. (12730)
- 36 (uter\$ adj2 malform\$).tw. (775)
- 37 (Uter\$ adj4 Neoplasm\$).tw. (842)
- 38 (uter\$ adj4 abnormalit\$).tw. (1035)
- 39 fibroid\$.tw. (5706)
- 40 or/7-39 (512038)
- 41 randomized controlled trial.pt. (458772)
- 42 controlled clinical trial.pt. (92329)
- 43 randomized.ab. (408806)

- 44 placebo.tw. (193271)
- 45 clinical trials as topic.sh. (183298)
- 46 randomly.ab. (288659)
- 47 trial.ti. (180948)
- 48 (crossover or cross-over or cross over).tw. (76033)
- 49 or/41-48 (1172279)
- 50 exp animals/ not humans.sh. (4446637)
- 51 49 not 50 (1078473)

Appendix 4. Embase search strategy

Searched from 1980 to 16 April 2018

OVID Platform

- 1 exp hysteroscopy/ (10442)
- 2 Hysteroscop\$.tw. (10344)
- 3 endoscop\$.tw. (272107)
- 4 exp endoscopy/ or exp urogenital endoscopy/ (538246)
- 5 or/1-4 (654400)
- 6 exp female infertility/ or exp infertility therapy/ (117458)
- 7 subfertil\$.tw. (6209)
- 8 Infertil\$.tw. (73959)
- 9 artificial insemination/ or exp fertilization in vitro/ or exp intracytoplasmic sperm injection/ or exp intrauterine insemination/ (71950)
- 10 (in vitro fertili\$ or intracytoplasmic sperm).tw. (32834)
- 11 (IVF or ICSI or IUI).tw. (43015)
- 12 artificial insemination.tw. (5647)
- 13 (intrauter* adj2 inseminat*).tw. (3417)
- 14 assisted conception.tw. (1601)
- 15 assisted reproduct*.tw. (19314)
- 16 or/6-15 (181531)
- 17 exp uterus myoma/ or exp myoma/ (34252)
- 18 exp leiomyoma/ (17459)
- 19 (myoma or myomectomy).tw. (8654)
- 20 septate uterus.tw. (626)
- 21 polypectomy.tw. (7240)
- 22 adhesiolysis.tw. (2445)
- 23 (remov\$ adj2 adhesion\$).tw. (253)
- 24 (?intrauter* adj2 adhesion\$).tw. (679)
- 25 (septoplast* or metroplast*).tw. (2357)
- 26 (sept* adj2 resect*).tw. (560)
- 27 Asherman* syndrome.tw. (411)
- 28 polyp\$.tw. (286769)
- 29 uterine septa.tw. (154)
- 30 uterine septum.tw. (469)
- 31 synech\$.tw. (9682)
- 32 Leiomyoma\$.tw. (15738)
- 33 (uter\$ adj4 malform\$).tw. (1402)
- 34 (Uter\$ adj4 Neoplasm\$).tw. (926)
- 35 (uter\$ adj4 abnormalit\$).tw. (1420)
- 36 fibroid\$.tw. (9428)
- 37 or/17-36 (342555)
- 38 5 and 16 and 37 (2475)
- 39 Clinical Trial/ (964209)

40 Randomized Controlled Trial/ (495134)
 41 exp randomisation/ (77876)
 42 Single Blind Procedure/ (31024)
 43 Double Blind Procedure/ (145965)
 44 Crossover Procedure/ (54970)
 45 Placebo/ (309585)
 46 Randomized controlled trial\$.tw. (179133)
 47 Rct.tw. (28028)
 48 random allocation.tw. (1767)
 49 randomly allocated.tw. (29351)
 50 allocated randomly.tw. (2307)
 51 (allocated adj2 random).tw. (794)
 52 Single blind\$.tw. (20651)
 53 Double blind\$.tw. (181005)
 54 ((treble or triple) adj blind\$.tw. (765)
 55 placebo\$.tw. (266160)
 56 prospective study/ (441083)
 57 or/39-56 (1888652)
 58 case study/ (53662)
 59 case report.tw. (350881)
 60 abstract report/ or letter/ (1032536)
 61 or/58-60 (1428530)

Appendix 5. CINAHL search strategy

Searched from 1961 to 16 April 2018

EBSCO Platform

S43 S30 AND S42 184

S42 S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 1,224,457

S41 TX allocat* random* 8,624

S40 (MH "Quantitative Studies") 19,276

S39 (MH "Placebos") 10,763

S38 TX placebo* 50,564

S37 TX random* allocat* 8,624

S36 (MH "Random Assignment") 46,918

S35 TX randomi* control* trial* 146,875

S34 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*)) 950,353

S33 TX clinic* n1 trial* 223,176

S32 PT Clinical trial 86,215

S31 (MH "Clinical Trials+") 238,828

S30 S6 AND S29 1,027

S29 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 24,606

S28 TX fibroid* 1,459

S27 TX (uter* N2 abnormalit*) 644

S26 TX (uter* N2 neoplasm*) 2,615

S25 TX (uter* malform*) 642

S24 TX Leiomyoma 3,066

S23 TX (uter* N4 polyp*) or TX (endometri* N4 poly*) 371

S22 TX (remov* N2 adhesion*) 28

S21 (MM "Adhesions") 637

S20 TX adhesiolysis 212
 S19 TX (sept* uter*) 727
 S18 TX (myoma or myomectomy) 1,107
 S17 (MM “Leiomyoma”) 2,182
 S16 (MM “Myoma+”) 184
 S15 TX (assisted conception) 827
 S14 TX (artificial insemination) 538
 S13 (MM “Insemination, Artificial”) 277
 S12 TX (IVF or ICSI) 2,283
 S11 TX (Reproducti* Technique*) 5,749
 S10 MH reproduction techniques 3,361
 S9 (MM “Fertilization in Vitro”) 1,923
 S8 TX subfertil* or TX infertil* 10,820
 S7 (MM “Infertility”) 4,677
 S6 S1 OR S2 OR S3 OR S4 OR S5 56,419
 S5 (MM “Endoscopy”) 8,846
 S4 TX endoscop* 55,025
 S3 TX Uteroscop* 1
 S2 TX Hysteroscop* 1,501
 S1 (MM “Hysteroscopy”) 659

Appendix 6. Web of Science search strategy

Searched 16 April 2018

Web Platform

TOPIC: (((((Hysteroscopy OR Uterine Endoscop* OR Uteroscop* OR Hysteroscopic Surg* OR (hysteroscopic AND (polypectom* OR myomectom* OR synechiolysis OR adhesiolysis OR metroplast* OR septoplast* OR septum resection*)))) AND (female AND (Subfertility OR Infertility OR Sterility)) AND ((Endometri* AND (polyp OR polyps)) OR Leiomyoma* OR Fibromyoma* OR Fibroid* OR fibromas OR Myoma* OR Synechiae OR ((Intrauterine OR uterine) AND adhesion*) OR (Asherman* AND Syndrome*) OR ((septa OR septum) AND (uterine OR intrauterine)) OR uterine diseases OR uterine neoplasms OR ((uterine OR intrauterine) AND (congenital abnormalities)) OR (Fertilization SAME “in Vitro”) OR IVF OR ICSI OR reproductive techniques OR embryo transfer OR zygote intrafallopian transfer OR ((intrauterine OR artificial) AND insemination))))))

DocType=All document types; Language=All languages

Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=2014-2018

Appendix 7. Items of data extraction

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
 - Participant recruitment
 - Participant inclusion and exclusion criteria
 - Allocation concealment
 - Blinding of participants and personnel
 - Blinding of outcome assessors
 - Completeness of outcome data
 - Selective outcome reporting
 - Other potential sources of bias
- Follow-up
 - Duration of follow-up
 - Type of follow-up
- Size of study
 - Number of women recruited
 - Number of women randomised
 - Number of women excluded
 - Number of women withdrawn and lost to follow-up
 - Number of women analysed
- Study setting
 - Single-centre or multicentre
 - Location
 - Timing and duration
- Diagnostic criteria
 - Screening by transvaginal ultrasound (TVS)
 - Screening by hysterosalpingography (HSG)
 - Screening by TVS and HSG
 - Screening by other ultrasound diagnostic procedures, e.g. saline infusion sonography or gel instillation sonography
 - Screening by hysteroscopy
 - Diagnosis confirmed by hysteroscopy and biopsy

4. Characteristics of the study participants

- Baseline characteristics
 - Age
 - Primary or secondary subfertility
 - Duration of subfertility
 - Diagnostic work-up: baseline follicle stimulating hormone, semen analysis, diagnosis of tubal pathology, confirmatory test of ovulation
 - Other contributory causes to subfertility than uterine factor
 - Previous treatments: in vitro fertilisation (IVF), intrauterine insemination (IUI) or other treatments
- 2. Treatment characteristics
 - IUI natural cycle
 - IUI controlled ovarian stimulation with antioestrogens or gonadotropins
 - IVF protocol and number of embryos transferred
 - Intracytoplasmic sperm injection protocol and number of embryos transferred
 - Detailed description of the hysteroscopic procedure

5. Interventions

- Total number of intervention groups
- Absence of other interventions in the treatment and control group

For each intervention and comparison group of interest

- Specific intervention
- Intervention details
- Timing of the intervention

6. Outcomes

- Outcomes and time points collected
- Outcomes and time points reported

Definition and unit of measurement for each of the following outcomes:

Primary outcomes

- Live birth delivery rate
- Hysteroscopy complication rate

Secondary outcomes

- Ongoing pregnancy rate
- Clinical pregnancy with foetal heartbeat
- Clinical pregnancy rate
- Miscarriage rate

For each outcome of interest:

- Sample size
- Missing participants
- Summary data for each intervention group in 2 × 2 table
- Estimate of effect with 95% confidence interval
- Subgroup analyses

7. Miscellaneous

- Funding source
- Key conclusions of the study authors
- Miscellaneous comments from the study authors
- References to other relevant studies
- Correspondence required
- Miscellaneous comments by the review authors

WHAT'S NEW

Date	Event	Description
20 June 2018	New citation required but conclusions have not changed	The conclusions of this review have not changed
17 June 2018	New search has been performed	Updated literature search from 1 January 2014 until 16 April 2018. No new studies included

HISTORY

Protocol first published: Issue 11, 2011

Review first published: Issue 1, 2013

Date	Event	Description
29 October 2014	New search has been performed	This review has been updated but no new studies were eligible for inclusion
29 October 2014	New citation required but conclusions have not changed	There was no change to our conclusions.
29 August 2014	Feedback has been incorporated	Feedback on clinical diversity in this review, received from Professor Hossam Shawki

CONTRIBUTIONS OF AUTHORS

JB: co-ordinated the writing of the protocol and review and its update.

SVW and MB: assisted in the literature search and study selection.

FB and TD: independently assessed the retrieved published reports for inclusion of potentially eligible studies.

JB and SW: independently extracted study data.

FB and BWM: gave advice on review methodology and content and critically appraised the Cochrane Review.

DECLARATIONS OF INTEREST

FB (principal investigator) and BWM (co-investigator) were involved in the design and conduct of the 'inSIGHT trial' (SIGNificance of Routine Hysteroscopy Prior to a First 'in Vitro Fertilization' Treatment Cycle: NCT 01242852), which was financially supported by ZonMw, a Dutch government operated consortium responsible for granting funds in the field of clinical practice research.

Thomas D'Hooghe is paid full time by Merck KGaA, Darmstadt, Germany as Vice-President and Head of Global Medical Affairs Fertility since October 1st 2015. He is also part time employed by KU Leuven (University of Leuven, Belgium) as Professor in Reproductive Medicine and by Yale University as Adjunct Professor Obstetrics and Gynecology. His co-authorship on the current paper is part of his academic activity, and Merck KGaA does not have marketed products related to hysteroscopy. Professor D'Hooghe's employment by Merck is not in breach of Cochrane's Commercial Sponsorship Policy (clause 2) as he does not have a real or potential financial interest in the outcome of this review. This matter was referred to Cochrane's Funding Arbiter for advice.

FB has received monetary compensation for the following: member of the external advisory board for Merck Serono and Ferring, the Netherlands; educational activities for Ferring BV, the Netherlands; consultancy work for Gedeon Richter, Belgium; strategic co-operation with Roche on automated anti-Müllerian hormone (AMH) assay development; and research co-operation with Ansh Labs.

BWM has received consultancy from ObsEva Geneva, Guerbet, and Merck; payment for review preparation from European Journal of Obstetrics and Gynecology and Reproductive Biology; and travel/accommodation/meeting expenses for various non-commercial scientific meetings.

JB, SW, SVW and MB do not have conflicts of interest for the research presented in this updated Cochrane Review.

The first published version of the present Cochrane Review has been part of a PhD thesis entitled "Studies on the effectiveness of endoscopic surgery in reproductive medicine" (dare.uva.nl/record/497164), which has been successfully defended at the faculty of Medicine of the University of Amsterdam, the Netherlands on 2 September 2014 by the first author (JB).

SOURCES OF SUPPORT

Internal sources

- CEBAM, Belgium.

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

At the 2014 update:

- As a result of further peer review, the objectives of the review have been rephrased. The descriptions in the [Types of interventions](#) and [Data synthesis](#) sections were modified accordingly. For both comparisons, we made a stratification according to the types of uterine pathology; for the second comparison, we made a clear distinction between IUI, IVF or ICSI.

- 'Summary of findings' tables using the GRADE approach were added.

- In the [Assessment of risk of bias in included studies](#) section of the review, the items 'blinding of participants and personnel' and 'blinding of outcome assessors' were reinserted as requested by the editorial reviewers. We assessed all six items including blinding of participants, personnel and outcome assessors in the final review as opposed to the protocol.

- In the [Assessment of heterogeneity](#) section of the review, we added the Q-statistic.

- In the [Subgroup analysis and investigation of heterogeneity](#) section of the review, we planned to conduct a further subgroup analysis based on the women's age.

At the 2018 update:

- We added a fourth exclusion criterion in the section [Types of participants](#): women of reproductive age with no major uterine cavity abnormalities detected by US, SIS, GIS, HSG, diagnostic hysteroscopy or any combination of these methods. The objective of this review was to assess the effectiveness of operative hysteroscopy in women with suspected uterine cavity abnormalities. The effectiveness of hysteroscopy in women without suspected uterine cavity abnormalities is the objective of a second Cochrane review. The addition of this fourth exclusion criterion is to emphasise the difference between the reviews since they include different study populations.

INDEX TERMS

Medical Subject Headings (MeSH)

*Hysteroscopy; Coitus; Endometrium; Fertilization in Vitro; Infertility [etiology; *surgery]; Insemination, Artificial [methods]; Leiomyoma [surgery]; Polyps [surgery]; Randomized Controlled Trials as Topic; Tissue Adhesions [surgery]; Uterine Diseases [*surgery]; Uterus [abnormalities]

MeSH check words

Female; Humans; Pregnancy