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 detectable 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 Cochrane Menstrual Disorders and Subfertility Specialised Register (6 August 2012), the Cochrane Central Register of Controlled Trials (*T he Cochrane Library* 2012, Issue 7), MEDLINE (1950 to October 2012), EMBASE (1974 to October 2012), CINAHL (from inception to October 2012) and other electronic sources of trials including trial registers, sources of unpublished literature and reference lists.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 January 2008 to October 2012) and we contacted experts in the field.

Selection criteria

Randomised comparisons between operative hysteroscopy versus control in women with otherwise unexplained subfertility or undergoing IUI, IVF or ICSI and suspected major uterine cavity abnormalities diagnosed by ultrasonography, saline infusion/gel instillation sonography, hysterosalpingography, diagnostic hysteroscopy or any combination of these methods. Primary outcomes were live birth and hysteroscopy complications. Secondary outcomes were pregnancy and miscarriage.

Data collection and analysis

Two 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 and neither reported the primary outcomes of live birth and complications from the procedure. In women with otherwise unexplained subfertility and submucous fibroids, there is no evidence of benefit with hysteroscopic myomectomy compared to regular fertility-oriented intercourse during 12 months for clinical pregnancy (odds ratio (OR) 2.4, 95% confidence interval (CI) 0.97 to 6.2, P = 0.06, 94 women) and miscarriage (OR 1.5, 95% CI 0.47 to 5.0, P = 0.47, 94 women) (very low-quality evidence). The hysteroscopic removal of polyps prior to IUI increases the odds of clinical pregnancy (experimental event rate (EER) 63%) compared to diagnostic hysteroscopy and polyp biopsy only (control event rate (CER) 28%) (OR 4.4, 95% CI 2.5 to 8.0, P < 0.00001, 204 women, high-quality evidence).

Authors' conclusions

Hysteroscopic myomectomy might increase the odds of clinical pregnancy in women with unexplained subfertility and submucous fibroids, but the evidence is at present not conclusive. The hysteroscopic removal of endometrial polyps suspected on ultrasound in women prior to IUI might increase the clinical pregnancy rate. More randomised studies are needed to substantiate the effectiveness of the hysteroscopic removal of suspected endometrial polyps, submucous fibroids, uterine septum or intrauterine adhesions 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

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, fibroids, septa or adhesions, may disturb this important event. The removal of these abnormalities by doing a so-called 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 intrauterine insemination or in vitro fertilisation. This review identified no studies reporting live birth as an outcome. We found one study on the removal of fibroids in women with unexplained infertility. It suggests that there might be a higher chance of conceiving after surgery compared to regular sexual intercourse for 12 months. Due to the low number of women (94) and the low number of pregnancies (30) the differences are not statistically significant. The quality of the study is very low. Therefore uncertainty remains about the real value of removal of fibroids in raising the chance of conception in women having difficulty becoming pregnant. We found only one study on hysteroscopy in 215 women with polyps who were to be treated with insemination for various fertility problems. The findings support an important increase in the pregnancy rates after the hysteroscopic removal of polyps. Although the quality of this study is high, further studies are needed to confirm this result. Neither of the two studies reported data on the surgical complications of hysteroscopy.

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

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

Operative hysteroscopy compared with control for unexplained subfertility associated with 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 one submucous fibroid ≤ 40 mm
Comparison: regular fertility-oriented intercourse

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	Myomectomy				
Clinical pregnancy ultrasound[1] 12 months	**Medium-risk population**		**OR 2.44** (0.97 to 6.17)	94 (1 study)	⊕◯◯◯ **very low**[2,3,4]	
	214 per 1000	**399 per 1000** (209 to 627)				
Miscarriage ultrasound[5] 12 months	**Medium-risk population**		**OR 1.54** (0.71 to 5.00)	94 (1 study)	⊕◯◯◯ **very low**[2,3,4]	
	119 per 1000	**172 per 1000** (88 to 403)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio

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

[1] A clinical pregnancy was defined by the visualisation of an embryo with cardiac activity at six to seven weeks' gestational age.
[2] Unclear allocation concealment.

[3] Wide confidence intervals.
[4] Unclear selective reporting and unclear whether there is other bias caused by imbalance in the baseline characteristics.
[5] Miscarriage was defined by the clinical loss of an intrauterine pregnancy between the 7^{th} and 12^{th} 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 (ART) (Zegers-Hochschild 2009). It is estimated that 72.4 million women are subfertile and that 40.5 million of these 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 is a basic step in the investigation of 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 (Saravelos 2008).

Ultrasonography (US), preferably transvaginally (TVS), is used to screen for possible endometrium or uterine cavity abnormalities in the work-up of subfertile patients. This evaluation can be expanded with hysterosalpingography (HSG), saline infusion/gel instillation sonography (SIS/GIS) and diagnostic hysteroscopy. Diagnostic hysteroscopy is generally considered as being 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 done for the purpose of 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 patient.

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 fibreoptic 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 to 4.0 mm. Operative hysteroscopy requires adequate visualisation through a continuous fluid circulation using an in- and an outflow channel. The outer diameters of modern operative hysteroscopes have been reduced to a diameter between 4.0 and 5.5 mm. The sheath system contains one or two 1.6 to 2.0 mm working channels for the insertion of small grasping or biopsy forceps, scissors, myoma fixation instruments, retraction loops, morcellators and aspiration cannulae, or unipolar or bipolar electrodiathermy instruments.

Most diagnostic and many operative procedures can be done in an office 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 set-up, special training of the surgeon and appropriate knowledge and management of complications (Campo 1999).

Although complications from hysteroscopy are rare, they may be potentially life threatening. A 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% versus 0.95%). The most common complication of both types of hysteroscopy was uterine perforation (0.13% for diagnostic; 0.76% for operative hysteroscopy). 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 interfere with the 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.

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). The chance for pregnancy is significantly lower in subfertile women with submucous fibroids compared to other causes of subfertility according to a 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; Tomaž evič 2010).

Why it is important to do this review

A National Institute for Health and Clinical 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 2004). There is, however, 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. Firstly, 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). Secondly, 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). Thirdly, 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 aims 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 those bound to undergo MAR. Since uterine cavity abnormalities might 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 suffering from 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 (IUI), in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI).

METHODS

Criteria for considering studies for this review

Types of studies

Inclusion criteria

- Only 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 considered to be eligible if the individually randomised women were the unit of analysis.
- Cross-over trials were also considered to be 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 prevailing 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 subfertility and intrauterine cavity abnormalities other than endometrial polyps, submucous fibroids, intrauterine adhesions and septate uterus, e.g. 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

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

- Randomised comparison between 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.
- Randomised comparison between 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

1. Effectiveness: live birth, defined as a delivery of a live fetus 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 (Zegers-Hochschild 2009).
2. Adverse events: hysteroscopy complications, defined as any complication due to hysteroscopy.

Secondary outcomes

3. Pregnancy
- Ongoing pregnancy, defined as a pregnancy surpassing the first trimester or 12 weeks of pregnancy.
- Clinical pregnancy with fetal heart beat, defined as a pregnancy diagnosed by US or clinical documentation of at least one fetus with a heart beat (Zegers-Hochschild 2009).
- Clinical pregnancy, defined as a pregnancy diagnosed by US visualisation of one or more gestational sacs or definitive clinical signs of pregnancy (Zegers-Hochschild 2009).

4. Adverse events: miscarriage, defined as the spontaneous loss of a clinical pregnancy before 20 completed weeks of gestation, or if gestational age is unknown a fetus with a weight of 500 g or less (Zegers-Hochschild 2009).

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

We planned to include the main outcome measures 'live birth', 'hysteroscopy complications' and 'miscarriage' in a 'Summary of findings' table (SoF). The SoF table was generated using GRADEpro software (GRADE profiler version 3.2.2). This table evaluated the overall quality of the body of evidence for the main review outcomes, using GRADE criteria (study limitations (i.e. risk of bias), consistency of effect, imprecision, indirectness and publication bias). We justified, documented and incorporated judgements about evidence quality (high, moderate, low or very low) into the

reporting of results for each outcome (Summary of findings for the main comparison; Summary of findings 2).
See the methods section of the protocol of this Cochrane review published in the *Cochrane Database of Systematic Reviews* (Bosteels 2011).

Search methods for identification of studies

See the Cochrane Menstrual Disorders and Subfertility Group (MDSG) for methods used in reviews, as stated in the MDSG Module.
See also the methods section of the protocol for this Cochrane review published in the *Cochrane Database of Systematic Reviews* (Bosteels 2011).
An experienced librarian at the Biomedical Library Gasthuisberg of the Catholic University of Leuven (Jens De Groot) developed the literature search strategy in liaison with the MDSG Trials Search Co-ordinator (Marian Showell).
Two people (JB and JK) 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. All the retrieved citations from MEDLINE, EMBASE, WoS, CENTRAL, the MDSG Specialised Register, BIOSIS PREVIEWS and handsearch-related articles have been merged and duplicates have been removed using specialised software (EndNote Web 3.5 - last done on 28 October 2012).

Electronic searches

We searched the following bibliographic databases, trial registers and websites: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 7) (Appendix 1), the Menstrual Disorders and Subfertility Group (MDSG) Specialised Register (Appendix 2), MEDLINE using PubMed (1950 to 27 October 2012) (Appendix 3) and EMBASE using EMBASE.com (1974 to 27 October 2012) (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* (version 5.1.0, Chapter 6, 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:

- Cochrane Database of Systematic Reviews (CDSR) in *The Cochrane Library* 2012, Issue 8 for published reviews to check for references to the included and excluded studies.
- Database of Abstracts of Reviews of Effectiveness (DARE) and the Health Technology Assessment Database (HTA Database) through the Centre for Reviews and Dissemination (from inception to 28 October 2012) (www.crd.york.ac.uk).
- National Guideline Clearinghouse (www.guideline.gov) for evidence-based guidelines (from inception to 28 October 2012).
- BIOSIS previews through ISI Web of Knowledge (http://isiwebofknowledge.com) and CINAHL (www.cinahl.com) through EBSCOHOST available at the Biomedical Library Gasthuisberg of the Catholic University of Leuven (from inception to 27 October 2012) (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 (http://clinicaltrials.gov/ct2/home) and the World Health Organization International Clinical Trials Registry Platform search portal (http://apps.who.int/trialsearch/) (from inception to 28 October 2012).
- Citation indexes: Science Citation Index through Web of Science (http://scientific.thomson.com/products/sci/) - SCI-EXPANDED (1955 to 27 October 2012) and Conference Proceedings Citation Index - Science (CPCI-S) (1990 to 27 October 2012) and Scopus (http://www.info.sciverse.com/scopus/) (from inception to 27 October 2012).
- Conference abstracts and proceedings on the ISI Web of Knowledge (http://isiwebofknowledge.com) applying 'SCI-EXPANDED' (1955 to 27 October 2012) and 'CPCI-S' (1990 to 27 October 2012) (Appendix 6).
- LILACS database, which is a source of trials from the Spanish and Portuguese speaking world (http://bases.bireme.br/cgi-bin/wxislind.exe/iah/online/?IsisScript=iah/iah.xis&base=LILACS&lang=i&form=F) (from inception to 28 October 2012).
- European grey literature through Open Grey database (from inception to 28 October 2012) (http://www.opengrey.eu/subjects/).
- General search engines: Turning Research into Practice (TRIP) database (www.tripdatabase.com), Google Scholar (http://scholar.google.be/advanced_scholar_search) and Scirus (http://www.scirus.com) (from inception to 28 October 2012).

Searching other resources

Two people (JB and JK) independently handsearched the reference lists of reviews, guidelines, included and excluded studies and other related articles for additional eligible studies. JB contacted the first or corresponding authors of included studies to ascertain if they were aware of any ongoing or unpublished trials.
We handsearched the American Society for Reproductive Medicine (ASRM) conference abstracts and proceedings (from 2008 to 30 October 2012) independently (JB and JK) since these were not covered in the MDSG register (after consultation with the MDSG Trials Search Co-ordinator).

JB contacted European experts and opinion leaders in the field of hysteroscopic surgery through a formalised project approved by the Board of the European Society of Gynaecological Endoscopy (ESGE) to ascertain if these experts were aware of any relevant published or unpublished studies.

Data collection and analysis

Selection of studies

Two people were responsible for independently selecting the studies (FB and TD). 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), 'excluded studies' (Characteristics of excluded studies), 'ongoing studies' (Characteristics of ongoing studies) studies or 'studies awaiting classification' (Characteristics of studies awaiting classification). Any disagreements between both review authors who are content experts were resolved through consensus or by a third review author with methodological expertise (BWM). 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 the disagreement was reported 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 Cochrane Menstrual Disorders and Subfertility Review Group.

Data extraction and management

Two people, 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 appendix 7 of the Cochrane protocol (Appendix 7). We pilot-tested the data extraction form and process by reviewing 10 randomly chosen reports of studies. In the pilot phase one retracted study report (Shokeir 2011) was consistently identified by the two review authors 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. 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). 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, the disagreement was reported in the review.

Assessment of risk of bias in included studies

Two authors (JB and SW) independently assessed the risk of bias of the included studies by using the Cochrane 'Risk of bias' assessment tool that considers the following criteria, listed in the *Cochrane Handbook for Systematic Reviews of Interventions* (version 5.1.0, Chapter 8, table 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; other potential sources of bias. As pre-specified and explained in the published protocol for this review (Bosteels 2011) the criteria 'blinding of participants and personnel' and 'blinding of outcome assessors' were not included in the 'Risk of bias' assessment. We justify this for the following two reasons. Blindness to whether an operative or diagnostic hysteroscopy was carried out in a trial is never possible for the surgeon; given the legal obligation to obtain fully informed consent before a surgical intervention, blinding of the patient is hardly possible in daily practice. Moreover, by selecting only 'hard outcomes' which are easy to ascertain, even unblinded observers of a given study participant are unlikely to disagree about whether or not these outcomes have occurred. Lack of blinding will not increase the risk of bias if follow-up is complete and outcomes are unequivocal (e.g. live birth). JB and SW assessed therefore only four of the six criteria in the Cochrane 'Risk of bias' tool; any disagreements were resolved by consensus or by discussion with a third review author (BWM). We fully described all judgements. The conclusions were presented in the 'Risk of bias' table (Characteristics of included studies) and incorporated 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 (M-H) odds ratios (OR). We presented 95% confidence intervals (95% 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 have 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 data (TTP). We planned reporting the data of those reports that failed to present additional data that could be analysed under 'other data'; we have not included TTP data in any meta-analysis.

Unit of analysis issues

All primary and secondary outcomes were expressed as per woman randomised. 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. Multiple live births and multiple pregnancies were counted as one live birth or one pregnancy event. We planned including 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 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 substantial differences in the analysis were found as compared to an available data analysis, we reported this in the final 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 by using the I^2 statistic combined with the Q-statistic. Cochran's Q test, a kind of Chi^2 statistic, is the classical measure to test significant heterogeneity. Cochran's Q test is calculated as the weighted sum of squared differences between individual study effects and the pooled effect across studies. The Q-statistic follows Chi^2 distribution with k-1 degree of freedom where k is the number of studies. $Q > k-1$ suggests statistical heterogeneity. A low P value of Cochran's Q test means significant heterogeneous results among different studies; usually, the P value at 0.10 is used as the cut-off. The Q-statistic has low power as a comprehensive test of heterogeneity especially when the number of studies is small. The Q-statistic informs us about the presence or absence of heterogeneity; it does not report on the extent of such heterogeneity. The I^2 statistic describes the percentage of variation across studies that is due to significant heterogeneity rather than random chance. It measures the extent of heterogeneity. An I^2 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 RevMan 5 (RevMan 2011), if there was evidence of substantial statistical heterogeneity.

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

JB entered the data and carried out the statistical analysis of the data using Review Manager 5 software (RevMan 5). 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 RevMan 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 stratum only. If no trials were retrieved 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 (Bosteels 2011).

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' in order 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 (Wamsteker 1998) as references when applicable.
- We planned to carry out subgroup analyses based on the patient 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 performed 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 were restricted to studies without high risk of bias;
- 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 odds ratio.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

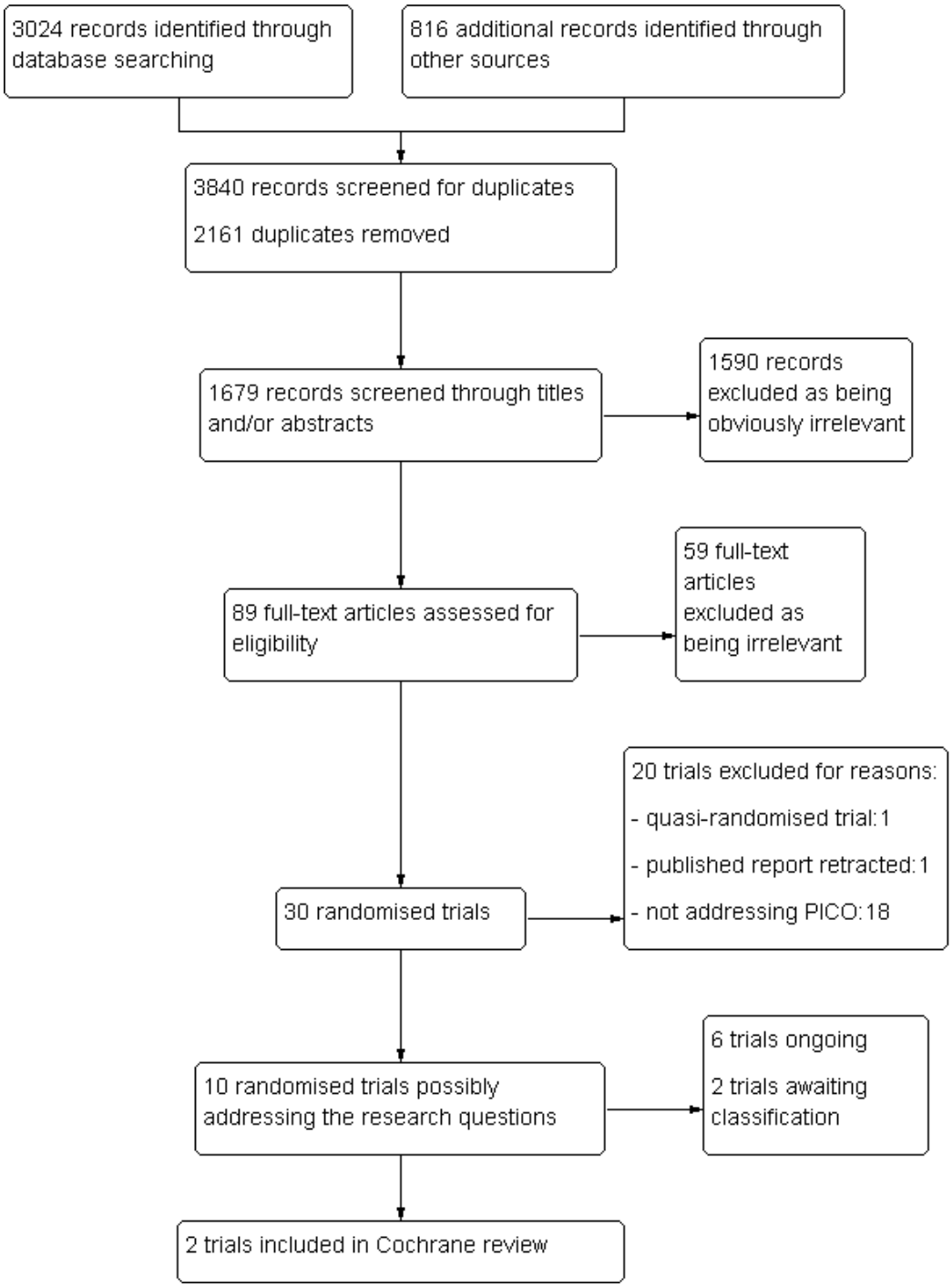
Results of the search

JB and JK scanned the titles and abstracts of the results of the search strings. The CENTRAL search produced 22 abstracts; there were 155 abstracts from the MDSG Specialised Register, 69 from MEDLINE, 248 from EMBASE, 210 from BIOSIS PREVIEWS and 60 from ISI Web of Science. An electronic search in DARE produced four abstracts; there was one guideline from National Guideline Clearinghouse, six from the metaRegister of controlled trials, eight from WHO ICTRP and 139 from TRIP/Google Scholar/Scirus. We identified 77 additional references in Scopus. No additional references were retrieved in CINAHL, LILACS and Open Grey. From handsearching reference lists and related articles 793 abstracts were identified. The handsearch of the proceedings of the American Society for Reproductive Medicine produced 21 abstracts; two abstracts were identified after contacting the experts of the European Society for Gynaecological Endoscopy (ESGE). We assessed one non-English language trial for inclusion (Trninić - Pjević 2011). An English translation of the summary of the Serbian abstract was available, suggesting that the study is a clinical controlled trial but it is not certain whether a random sequence generation was used or not. Since no further clarification could be obtained from the authors of the study we categorised this trial as 'awaiting classification' (Characteristics of studies awaiting classification).

After combining 3024 records identified from electronic searches with 816 additional records through searching other sources, we screened 3840 records for duplicates by using a specialised software program (EndNote Web 3.5). After the removal of 2161 duplicate references, we screened 1679 records through titles and/

or abstracts; 1590 records were excluded as being obviously irrelevant. We assessed 89 full-text articles for eligibility: 59 full-text articles were excluded because they presented data from observational studies or were narrative reviews. The remaining full-text articles identified 30 randomised controlled trials on hysteroscopic interventions in subfertile women; only two studies were included (Characteristics of included studies), 20 were excluded (Characteristics of excluded studies), two are awaiting classification (Characteristics of studies awaiting classification) and six are ongoing (Characteristics of ongoing studies).
See: PRISMA flow chart (Figure 1).

Figure 1. PRISMA study flow diagram.



Included studies

Study design and setting

Two parallel-design randomised controlled trials were included in the review.

Both were single-centre studies, one conducted in Italy (Casini 2006) and the other in Spain (Pérez-Medina 2005).

Participants

One study (Casini 2006) included 94 women with submucous fibroids and otherwise unexplained subfertility. 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. Transvaginal ultrasonography was performed in order to diagnose the presence of uterine fibroids. All women who were found to be affected by uterine fibroids excluding all other causes of infertility were asked to participate in the study. Only women aged $\leq$ 35 years with a problem of subfertility for at least one year and the presence of one fibroid of diameter $\leq$ 40 mm were selected for randomisation. Patients 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 > 40 mm, body weight > 20% of normal weight; and use of medication containing oestrogens, progestins or androgens within eight weeks prior to the study.

The second study (Pérez-Medina 2005) included 215 women with unexplained, male or female factor infertility for at least 24 months bound to undergo intrauterine insemination with a sonographic diagnosis of endometrial polyps. There were 101 women in the intervention group and 103 women in the control group; 11 women were lost to follow-up, six in the intervention group and five in the control group. The mean participant age was 31 years (range 27 to 35). All women suffered from 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 FSH, as well as women with a male partner with azoospermia, were excluded from randomisation.

Details of the inclusion and exclusion criteria are found in Characteristics of included studies.

Interventions

In one trial (Casini 2006) the intervention group was treated with hysteroscopic surgery to remove the fibroids; transvaginal ultrasonography was done three months after the procedure for control. Women in the intervention group were suggested to abstain from having 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 regular fertility-oriented intercourse. Both groups were monitored for up to 12 months after study commencement.

In the second trial (Pérez-Medina 2005) all hysteroscopic interventions were done in an outpatient office setting under local anaesthesia by one gynaecologist. In the intervention group the endometrial polyps suspected on Doppler ultrasound were extracted by means of a 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 recombinant follicle stimulating hormone (FSH) 50 IU 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 ultrasound 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 of the control group were scheduled to receive four cycles of IUI, using subcutaneous injections of recombinant follicle-stimulating hormone (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 (Casini 2006) measured two secondary outcomes, clinical pregnancy and miscarriage rate. 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 (Pérez-Medina 2005) reported only one secondary outcome, the clinical pregnancy rate. This was defined by a pregnancy diagnosed by ultrasound visualisation of one or more gestational sacs.

A plausible explanation for the failure to report on the live birth rate was given by the study authors of one trial (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 (Casini 2006) could not be contacted successfully for further clarification on the absence of reporting the primary outcomes.

Excluded studies

We excluded 20 trials on hysteroscopic interventions for various reasons.

One trial (Shokeir 2010) was excluded since the main published report was retracted at the request of the editor of the publishing journal as it duplicates parts of a paper on a different topic that had already appeared in another journal published years before (Pérez-Medina 2005). One trial (Pabuccu 2008) is a quasi-randomised trial. We excluded 18 trials because they did not address the pre-specified PICO research questions of this Cochrane review. Five trials (Aghahosseini 2012; Demirol 2004; El-Nashar 2011; Rama Raju 2006; Shawki 2010) studied the effectiveness of hysteroscopy in subfertile women bound to undergo IVF or ICSI treatment with unsuspected or no uterine cavity abnormalities. Three trials (Lieng 2010a; Muzii 2007; van Dongen 2008) were excluded because the study population included women not of reproductive age suffering from gynaecological problems other than subfertility. One trial (Vercellini 1993) was excluded because the study population included only women with repeated miscarriage. Six trials (Acunzo 2003; Amer 2010; De Iaco 2003; Di Spiezio Sardo 2011; Guida 2004; Tonguc 2008) studied the effectiveness of adjunctive therapies (hyaluronic acid gel, amnion graft, cyclical hormone replacement therapy alone or intrauterine device alone or both co-treatments combined) for the prevention of intrauterine adhesions following hysteroscopic adhesiolysis. Three trials (Colacurci 2007; Darwish 2008; Parsanezhad 2006) compared different surgical techniques for treating uterine septum in a mixed study population of women suffering from subfertility or recurrent pregnancy loss.

See the table Characteristics of excluded studies.

Studies awaiting classification

Two trials are awaiting classification (Pansky 2009; Trninić -Pjević 2011). One trial (Pansky 2009) is completed but no published report could be retrieved from the literature search and we failed to contact the study authors. A second trial (Trninić -Pjević 2011) published in a non-English journal is a clinical controlled trial with unclear random sequence generation. We failed to contact the study authors successfully.

See the table Characteristics of studies awaiting classification.

Ongoing studies

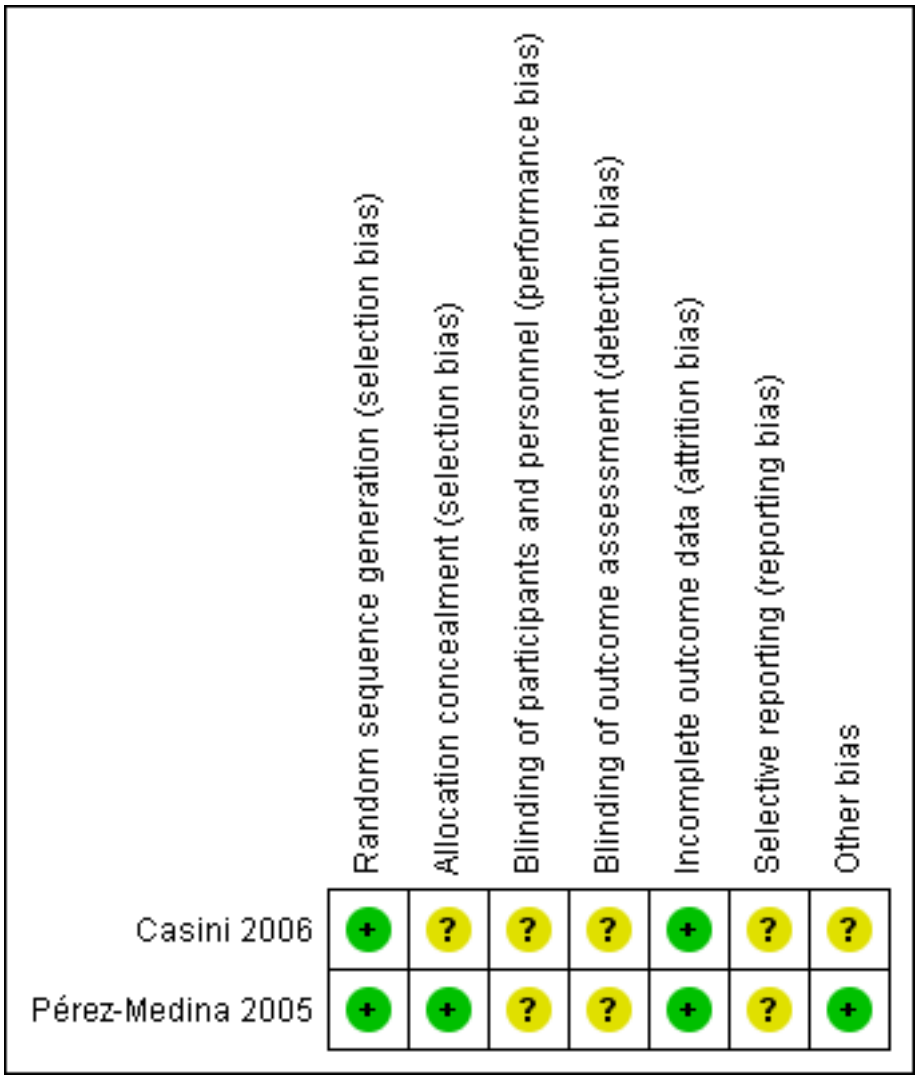
Six trials are ongoing (Broekmans 2010; El-Khayat 2012; El-Toukhy 2009; Maramazi 2012; Revel 2011; Sohrabvand 2012).

See the table Characteristics of ongoing studies.

Risk of bias in included studies

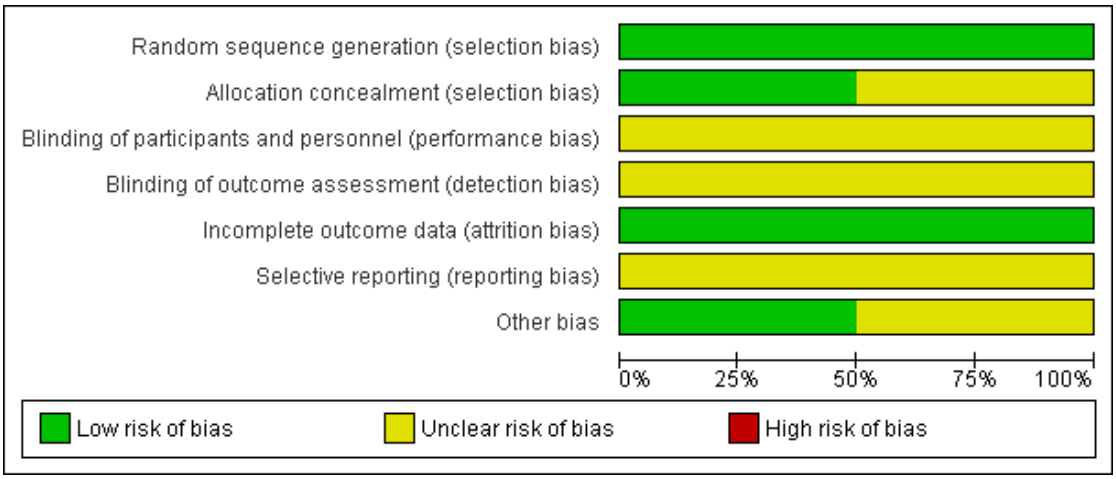
See the 'Risk of bias' summary for the review authors' judgements about each risk of bias item in the included study (Figure 2).

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



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 included in the Cochrane review (Casini 2006; Pérez-Medina 2005) to be at low risk of selection bias related to random sequence generation, as both used computerised random numbers tables.

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

Blinding

The risk of bias items 'blinding of participants and personnel' and 'blinding of outcome assessors' were not assessed for either of the included studies as pre-specified and justified in the published protocol for this review (see Bosteels 2011 and Assessment of risk of bias in included studies). The editorial reviewers nevertheless insisted on keeping the two items of blinding activated in the 'Risk of bias' tool in the final review while indicating in the 'Risk of bias' table of included studies that they were not assessed. Given that all six items were consequently presented in the 'Risk of bias' summary and the 'Risk of bias' graph, we decided to categorise the two non-assessed items as 'at unclear risk of bias' rather than 'high risk of bias' since a lack of blinding will not increase the risk of bias in studies with a complete follow-up and unequivocal outcomes. The items were not assessed as 'at low risk of bias' since we aimed to avoid upgrading of the quality of evidence based on items which were not assessed. A sensitivity analysis comparing the use of 'at low risk of bias' rather than 'at unclear risk of bias' did not affect the grading of the quality of the evidence for the two included studies.

Incomplete outcome data

We judged both studies included in the Cochrane review to be at low risk of attrition bias. One study (Casini 2006) reported outcome data of all randomised women. The second study (Pérez-Medina 2005) analysed the majority of women randomised (95%). 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 included in the review (Casini 2006; Pérez-Medina 2005) to be at unclear risk of reporting bias. No protocols were available for further analysis for either trial. All outcomes reported in the results sections were clearly pre-specified in the methods sections of the published study reports of both trials. Both studies (Casini 2006; Pérez-Medina 2005) 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. A plausible explanation was given by the contact author of one study (Pérez-Medina 2005); nevertheless 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). Moreover no data on adverse

outcomes such as miscarriage or hysteroscopy complications were reported in one trial (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 mean ages and duration of infertility in the intervention and control group of women with submucous fibroids were not reported; we failed to obtain these data from the study authors given that we were unsuccessful in contacting them. It is unclear whether there might be imbalance in the baseline characteristics between the comparison groups in this randomised trial (Casini 2006). We judged the second study (Pérez-Medina 2005) to be at low risk of other potential sources of bias since there was no evidence of baseline imbalance in the patient characteristics between the two comparison groups.

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

Effects of interventions

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

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

Endometrial polyps

No studies were retrieved.

Submucous fibroids

We retrieved only one study comparing hysteroscopic myomectomy versus regular fertility-oriented intercourse in women with unexplained subfertility and submucous fibroids only or combined with intramural fibroids (Casini 2006).

Primary outcomes

1.1. Live birth

There were no data for this primary outcome.

1.2. Adverse events: hysteroscopy complications

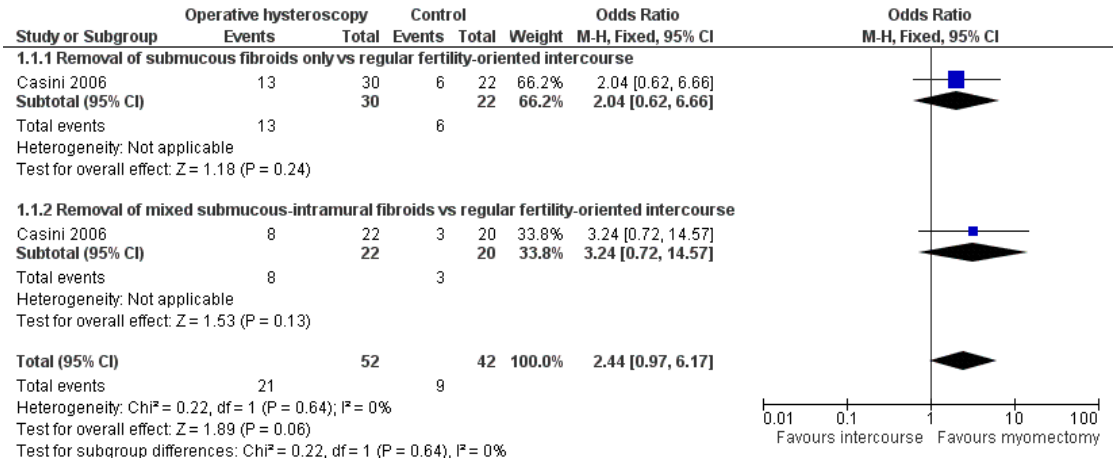
There were no data for this primary outcome.

Secondary outcomes

1.3. Clinical pregnancy

In women with otherwise unexplained subfertility for at least one year and one submucous fibroid of diameter $\leq$ 40 mm, there is no evidence for an effect favouring the removal of the fibroid by hysteroscopy compared to regular fertility-oriented intercourse for the secondary outcome of clinical pregnancy. Although hysteroscopic myomectomy tends to increase the odds of clinical pregnancy, the difference between the comparison groups is not statistically significant (odds ratio (OR) 2.4, 95% confidence interval (CI) 0.97 to 6.2, P = 0.06, one randomised controlled trial (RCT), 94 women) (Analysis 1.1; Figure 4). Considering the minimally important clinical difference (MICD), we pre-specified in the protocol (Bosteels 2011) that a MICD of 5% for the live birth rate would be considered as being relevant for the benefits of the intervention. The data for the one secondary outcome studied indicate a clinically important difference of 18% (95% CI 0% to 37%, P = 0.05) between the two comparison groups. This is a post hoc analysis. Although there might be a clinically relevant increase in the clinical pregnancy rate after hysteroscopic removal of submucous fibroids in women with otherwise unexplained subfertility compared to expectant management, there is uncertainty concerning the true point estimate of the clinical effect due to imprecision.

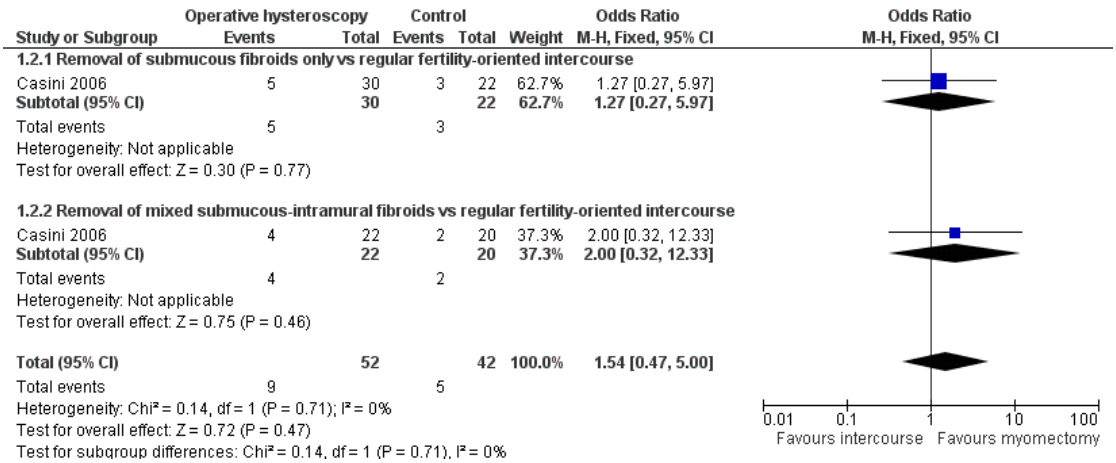
Figure 4. Forest plot of comparison: 1 Hysteroscopic myomectomy vs regular fertility-oriented intercourse in women with unexplained subfertility and submucous fibroids.Outcome: 1.1 Clinical pregnancy.



1.4. Adverse events: miscarriage

There is no evidence for an effect of the hysteroscopic removal of one submucous fibroid of diameter ≤ 40 mm in subfertile women with otherwise unexplained subfertility compared to regular fertility-oriented intercourse for the secondary outcome of miscarriage (OR 1.5, 95% CI 0.47 to 5.00, P = 0.47, one RCT, 94 women) (Analysis 1.2; Figure 5).

Figure 5. Forest plot of comparison: 1 Hysteroscopic myomectomy vs regular fertility-oriented intercourse in women with unexplained subfertility and submucous fibroids. Outcome: 1.2 Miscarriage.



Subgroup analyses

No subgroup analyses across studies could be done to assess any overestimation of treatment effect or reporting bias due to the limited number of studies.

One pre-specified 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 is no evidence for an effect favouring the hysteroscopic removal of one submucous fibroid ≤ 40 mm in subfertile women with otherwise unexplained subfertility compared to regular fertility-oriented intercourse for the secondary outcome clinical pregnancy in the 'submucous only' subgroup (OR 2.0, 95% CI 0.62 to 6.7, P = 0.24, one RCT, 52 women) or the 'mixed submucous-intramural' subgroup (OR 3.2, 95% CI 0.72 to 15, P = 0.13, one RCT, 42 women); the tests for subgroup differences demonstrated no evidence of statistical heterogeneity (Chi^2 = 0.22, df = 1 (P = 0.64), I^2 = 0%). There were no differences concerning the hysteroscopic removal of one submucous fibroid ≤ 40 mm in subfertile women with otherwise unexplained subfertility compared to regular fertility-oriented intercourse for the secondary outcome miscarriage in the 'submucous only' subgroup (OR 1.3, 95% CI 0.27 to 6.0, P = 0.77, one RCT, 52 women) or the 'mixed submucous-intramural' subgroup (OR 2.0, 95% CI 0.32 to 12, P = 0.46, one RCT, 42 women); the tests for subgroup differences demonstrated no evidence of statistical heterogeneity (Chi^2 = 0.14, df = 1 (P = 0.71), I^2 = 0%).

Sensitivity analyses

No sensitivity analyses could be done for live birth due to the lack of data for this primary outcome. Sensitivity analysis comparing the use of risk ratio rather than odds ratio as the effect measure did not affect the statistical significance of the main analysis for the secondary outcomes 'clinical pregnancy' (P = 0.07) and 'miscarriage' (P = 0.47). Sensitivity analysis comparing the inclusion of women with mixed intramural-submucous fibroids, rather than submucous fibroids only, did not affect the statistical significance of the main analysis for the secondary outcomes 'clinical pregnancy' (P = 0.06) (Analysis 1.1) and 'miscarriage' (P = 0.47) (Analysis 1.2).

Uterine septum

No studies were retrieved.

Intrauterine adhesions

No studies were retrieved.

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

Endometrial polyps prior to intrauterine insemination (IUI)

We retrieved only one study comparing 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

2.1. Live birth

There were no data for this primary outcome.

2.2. Adverse events: hysteroscopy complications

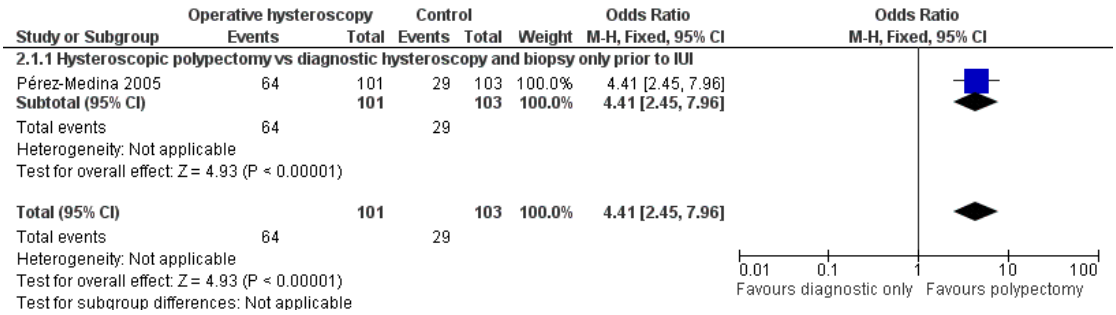
There were no data for this primary outcome.

Secondary outcomes

2.3. Clinical pregnancy

The hysteroscopic removal of polyps with a mean size of 16 mm, detected by Doppler ultrasonography in women with unexplained, male or female factor infertility for at least 24 months bound to undergo IUI, increases the odds of clinical pregnancy compared to diagnostic hysteroscopy and biopsy only (OR 4.4, 95% CI 2.5 to 8.0, P < 0.00001, one RCT, 204 women) (Analysis 2.1; Figure 6). The number needed to treat to benefit is 3 (95% CI 2 to 4). These results are based on an 'available data' analysis. The data for the one secondary outcome studied indicate a clinically important difference of 35% (95% CI 22% to 48%, P < 0.00001) between the two comparison groups favouring hysteroscopic polypectomy. There is evidence of a clinically important increase of the clinical pregnancy rate favouring hysteroscopic polypectomy compared to diagnostic hysteroscopy and polyp biopsy. This is a post hoc analysis, which was not pre-specified by the authors of the primary study.

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



2.4. Adverse events: miscarriage

There were no data for this secondary outcome.

Subgroup analyses

Although no subgroup analyses across studies were done to assess any overestimation of treatment effect or reporting bias given the limited number of studies, we did two subgroup analyses within the included study.

A first pre-specified subgroup analysis studied the effect of polyp size on the secondary outcome of clinical pregnancy. On histopathological examination the mean size of the polyps removed was 16 mm (range 3 to 24 mm). In the primary study the effect of the polyp size on the clinical pregnancy rate was studied in the intervention group. The data were analysed based on the size of the removed polyps, subdivided into four groups based in their quartiles (< 5 mm, 5 to 10 mm, 11 to 20 mm and > 20 mm); the differences between these four subgroups within this study were not statistically significant (P = 0.32) (Table 1). There is no evidence of an effect of the 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 increases the odds of clinical pregnancy 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, one study, 204 women, available data analysis). The number needed to treat to benefit after hysteroscopic polypectomy while waiting for further treatment with gonadotropin and IUI is 4 (95% CI 3 to 6). In women who started gonadotropin and IUI treatment the pregnancy rates per woman were 49% and 26% in the intervention and control group respectively, calculated from data in the published report of the primary study (Pérez-Medina 2005). Hysteroscopic polypectomy increases the odds of clinical pregnancy 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, one RCT, 172 women, available data analysis). The number needed to treat to benefit when treated with gonadotropin and IUI after a prior hysteroscopic polypectomy is 4 (95% CI 3 to 12). We judged this to be an honest and sensible post hoc 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 performed. Longer series are needed to verify these results*".

Sensitivity analyses

No sensitivity analyses were done for the outcome of live birth due to the lack of data for this primary outcome. Sensitivity analysis comparing the use of risk ratio rather than odds ratio as the effect measure did not affect the statistical significance of the main analysis for the secondary outcome 'clinical pregnancy' (P < 0.00001) (Analysis 2.1). A sensitivity analysis comparing an intention-to-treat 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, one 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 (IVF)

No studies were retrieved.

Endometrial polyps prior to intracytoplasmic sperm injection (ICSI)

No studies were retrieved.

Submucous fibroids prior to IUI

No studies were retrieved.

Submucous fibroids prior to IVF

No studies were retrieved.

Submucous fibroids prior to ICSI

No studies were retrieved.

Uterine septum prior to IUI

No studies were retrieved.

Uterine septum prior to IVF

No studies were retrieved.

Uterine septum prior to ICSI

No studies were retrieved.

Intrauterine adhesions prior to IUI

No studies were retrieved.

Intrauterine adhesions prior to IVF

No studies were retrieved.

Intrauterine adhesions prior to ICSI

No studies were retrieved.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Operative hysteroscopy compared with control for suspected major uterine cavity abnormalities prior to medically assisted reproduction

Patient or population: subfertile women with endometrial polyps diagnosed by ultrasonography prior to treatment with gonadotropin and intrauterine insemination
Settings: infertility unit of a university tertiary hospital in the Spanish capital Madrid
Intervention: hysteroscopic polypectomy using a 5.5 mm continuous flow office hysteroscope with a 1.5 mm scissors and forceps
Comparison: diagnostic hysteroscopy using a 5.5 mm continuous flow office hysteroscope and polyp biopsy

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				
Clinical pregnancy ultrasound[1] *4IUIcycles*	**Low-risk population**[2]		**OR 4.41** (2.45 to 7.96)	204 (1 study)	⊕⊕⊕⊕ **high**[5,6]	
	250 per 1000	**595 per 1000** (450 to 726)				
	Medium-risk population[3]					
	366 per 1000	**718 per 1000** (586 to 821)				
	High-risk population[4]					
	528 per 1000	**831 per 1000** (733 to 899)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio

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

[1] Clinical pregnancy was defined by the presence of at least one gestational sac on ultrasound.
[2] Based on the clinical pregnancy rate per woman after 4 cycles gonadotropins and IUI for male factor subfertility based on data from Bensdorp 2007.
[3] Based on the clinical pregnancy rate per woman after 4 cycles gonadotropins and IUI for unexplained subfertility based on data from Veltman-Verhulst 2012.
[4] Based on the clinical pregnancy rate per woman after 4 cycles gonadotropins and IUI for female factor subfertility based on data from Spiessens 2003.
[5] There was some potential for reporting bias.
[6] Large treatment effect in the absence of plausible confounders.

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 medically assisted reproduction (intrauterine insemination (IUI), in vitro fertilisation (IVF) and intracytoplasmic sperm injection (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 major randomised comparison is 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 ultrasonography (US), saline infusion/gel instillation sonography (SIS, GIS), hysterosalpingography (HSG), diagnostic hysteroscopy or any combination of these methods. The second randomised comparison is operative hysteroscopy versus control in women undergoing medically assisted reproduction (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.

We critically appraised one single trial (Casini 2006) comparing hysteroscopic removal of one submucous fibroid with a diameter $\leq$ 40 mm in women aged $\leq$ 35 years with otherwise unexplained subfertility versus regular fertility-oriented intercourse for a period of 12 months. There is no evidence of an effect favouring the removal of submucous fibroids by hysteroscopy in women with otherwise unexplained subfertility compared to expectant management for the secondary outcome of clinical pregnancy. We did not retrieve any trials on operative hysteroscopy versus control in women with otherwise unexplained subfertility and suspected endometrial polyps, intrauterine adhesions or septate uterus.

We found only one single trial (Pérez-Medina 2005) for the second category of randomised interventions. According to the results of the randomised comparison 'hysteroscopic polypectomy versus diagnostic hysteroscopy comparison in subfertile women with suspected endometrial polyps bound to undergo IUI', there is evidence for a clinically relevant and statistically significant increase in the odds of clinical pregnancy favouring the hysteroscopic removal of polyps with a mean size of 16 mm (range 3 to 24 mm). There were no data for the primary outcomes of live birth and hysteroscopy complications and the secondary outcome of miscarriage. The increase in clinical pregnancies after hysteroscopic polypectomy might be mainly due to a higher proportion of spontaneous conceptions before starting IUI and to a lesser, but still clinically relevant, extent to a higher odds of conceiving after starting gonadotropin treatment and IUI. The results of this sensible post hoc subgroup analysis should be interpreted with caution; at present no definitive conclusions can be made concerning the timing of the hysteroscopic intervention in relationship to the subsequent IUI treatment. There is no evidence for an effect of the size of the polyps on the outcome clinical pregnancy, but given the limited numbers this subgroup analysis should equally be interpreted with caution. No data on the polyp size were available from the control group: given the arbitrary distinction between biopsying or removing a very small polyp, the probability that the true treatment effect of hysteroscopic polypectomy might even have been underestimated can neither be proven nor ruled out.

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 is very limited. We found no trials on the hysteroscopic treatment of endometrial polyps, intrauterine adhesions or septa compared to a control intervention in women with otherwise unexplained subfertility. The only included study in this category fails 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 medically assisted reproduction is incomplete since data have been found only for subfertile women with suspected endometrial polyps prior to IUI. No data were retrieved on the effectiveness of operative hysteroscopy versus control in subfertile women with other suspected major cavity abnormalities such as submucous fibroids, intrauterine adhesions or septa prior to IUI or other techniques such as IVF or ICSI for all outcomes. Moreover for the randomised comparison hysteroscopic polypectomy versus diagnostic hysteroscopy prior to IUI no data are available for the primary outcomes. The evidence retrieved is by consequence insufficient to address all the objectives of the present Cochrane review.

The lack of statistical significance of the differences between the comparison groups in the trial of hysteroscopic myomectomy in women with submucous fibroids and otherwise unexplained subfertility does not exclude the possibility of a clinically relevant benefit favouring hysteroscopic surgery. It is generally accepted that submucous fibroids are very likely to interfere with normal fertility (Pritts 2001; Pritts 2009). In everyday practice the majority of skilled hysteroscopists 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. Although the results of the trial on hysteroscopic polypectomy (Pérez-Medina 2005) are relevant for everyday practice, one-third of the randomised women treated by IUI suffered from ovulatory

disorder. 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 study 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 and Table 3. See also Summary of findings for the main comparison and Summary of findings 2.

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

Using the GRADE tool as implemented in GRADE profiler, we graded the evidence of the first trial on hysteroscopic myomectomy (Casini 2006) as 'very low'. It is a small study with few events. The key methodological limitations of this study are twofold: there is uncertainty about allocation concealment and it is unclear whether there was imbalance in the baseline characteristics of the study groups. Moreover, the results are imprecise given the wide confidence intervals of the point estimate of the treatment effect. The effect of imprecision is to make the observed association closer to the null value than is the true association. The pre-planned subgroup analysis in terms of removal of submucous fibroids only or mixed-submucous intramural fibroids showed no evidence for an effect favouring the removal of fibroids compared to regular fertility-oriented intercourse; the absence of a treatment effect is consistent with the findings for the removal of submucous fibroids 'overall'. Although the interpretation of the statistical analysis of subgroups is problematic, there is no evidence of serious inconsistency.

The evidence of the second trial on hysteroscopic polypectomy (Pérez-Medina 2005) was graded as 'high': despite some potential for reporting bias (see Assessment of risk of bias in included studies) we upgraded the quality of the evidence of this study given the strong association provided by the magnitude of the treatment effect (risk ratio (RR) > 2; see the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.1.0 - section 12.2.3, Higgins 2011). This study had adequate statistical power to detect a difference between the comparison groups. There was no evidence for a dose-response relationship between the size of the polyps and the treatment effect of the hysteroscopic polypectomy according to the only pre-specified subgroup analysis. These findings should nevertheless be interpreted with great caution. According to a sensible post hoc analysis the treatment effect of hysteroscopic polypectomy is consistent among the subgroups of women waiting to be treated after hysteroscopy with gonadotropins and IUI and those who started gonadotropin treatment and IUI. Nevertheless, the use of post hoc analyses looking at subgroups after the trial has been conducted is open to potential problems of multiple comparisons and comparisons between non-randomised groups.

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 aimed to carry out a comprehensive literature search using a search strategy which 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 do not address the particular research questions pre-specified in the protocol (see Characteristics of excluded studies).

Agreements and disagreements with other studies or reviews

There are two systematic reviews on fibroids and subfertility (Pritts 2001; Pritts 2009). We refer to the data in the most recent review since the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines for systematic reviews of observational studies were followed (Pritts 2009). Two types of observational studies were identified: those controlling with women having fibroids in situ, and those using subfertile women without fibroids as control participants. If fibroid removal is beneficial, women treated by myomectomy would be expected to have higher pregnancy rates and lower miscarriage rates than those with fibroids in situ. In women with submucous fibroids, the clinical pregnancy rates were higher in the myomectomy group (RR 2.0, 95% CI 1.1 to 3.8, two studies, P = 0.028). The differences between both groups for the ongoing pregnancy/live birth rates failed to reach statistical significance (RR 2.6, 95% CI 0.92 to 7.6, one study, P > 0.05). There was no evidence for differences in the miscarriage rates between both groups (RR 0.77, 95% CI 0.36 to 1.7, one study, P > 0.05). When the control group consists of subfertile women without fibroids, myomectomy might be expected (if beneficial) to normalise the rates compared with controls. For women with submucous fibroids treated by hysteroscopic myomectomy, there was no evidence for statistically significant differences in clinical pregnancy rates (RR 1.5, 95% CI 1.0 to 2.4, two studies, P > 0.05), ongoing pregnancy/live birth rates (RR 1.1, 95% CI 1.0 to 1.3, three studies, P > 0.05) and miscarriage rates (RR 1.2, 95% CI 0.47 to 3.2, two studies, P > 0.05) compared to subfertile women without submucous fibroids. Meta-regression demonstrated that the study quality scores did not significantly affect the observed effect in the meta-analyses. Furthermore, sensitivity analyses comparing the use of the studies with the highest study quality did not affect the statistical significance of the main results compared to the use of all the retrieved studies, irrespective of the study quality. There was no evidence of publication bias in the systematic review of the literature done by this research group. The authors concluded that the fertility outcomes are decreased in women with submucosal fibroids, and removal is likely to benefit the reproduc-

tive outcome.

The results of the trial on the effectiveness of hysteroscopic polypectomy prior to IUI are consistent with the findings of two recently published observational studies. The first study planned to evaluate the effect of the presence of endometrial polyps on pregnancy rates and how polypectomy could affect pregnancy rates in 171 women scheduled for IUI (Kalampokas 2012). The presence of an endometrial polyp was diagnosed during the infertility evaluation. The study group consisted of 86 women who, following the diagnosis of endometrial polyp, agreed to have the polyps removed hysteroscopically prior to the IUI. The control group consisted of 85 women who, despite the fact that the presence of an endometrial polyp was previously diagnosed and its removal suggested, elected not to have the polyp removed. There was a statistically significant difference in cumulative pregnancy rates between the two groups, favouring hysteroscopic polypectomy. The authors concluded that hysteroscopic polypectomy appears to improve fertility in women with otherwise unexplained infertility. The second study, a prospective clinical controlled study including 120 women with endometrial polyps, aimed to study whether polypectomy before intrauterine insemination achieved better pregnancy outcomes than no intervention (Shohayeb 2011). All patients were scheduled to receive four cycles of IUI in both groups within 12 months duration. The first IUI cycle was planned after three menstrual cycles in both groups. Cumulative pregnancy rate in both groups after four IUI cycles was 23 (38.3%) in the study group and 11 (18.3%) in the control group (P = 0.015). The authors concluded that persistent endometrial polyps are likely to impair reproductive performance and that hysteroscopic polypectomy before IUI could be considered as an effective intervention. A systematic review (Lieng 2010b) included 11 studies in 935 subfertile women with endometrial polyps: one randomised controlled trial (Pérez-Medina 2005), three clinical controlled studies and seven observational studies (three retrospective, one prospective and three undetermined). Although there was no evidence for an effect favouring hysteroscopic polypectomy on the IVF outcomes according to two smaller non-randomised observational studies, the limited evidence suggests a favourable outcome on pregnancy rates in subfertile women with endometrial polyps. Due to the clinical diversity formal meta-analysis was rightfully judged to be inappropriate. The methodology for meta-analysis of observational studies proposed by The Cochrane Collaboration was not followed (no formal appraisal of the risk of bias, no study of the effect of confounders, no formal assessment of publication bias); therefore, the authors' conclusion should be interpreted with great caution.

AUTHORS' CONCLUSIONS

Implications for practice

There might be a clinically relevant increase in the odds of conceiving by removing submucous fibroids in women with otherwise unexplained subfertility compared to expectant management. The differences in clinical pregnancy rates between both comparison groups in the single published randomised trial were not statistically significant due to limited numbers; the level of evidence provided by this single small study was graded as very low.

Before treating subfertile women with a sonographic diagnosis of endometrial polyps with gonadotropins combined with intrauterine insemination for unexplained, male or female factor infertility for at least 24 months, it may be advisable to perform a hysteroscopic polypectomy to improve the chance of conceiving. The level of evidence provided by this single study was graded as high.

Implications for research

The evidence retrieved from the limited number of randomised studies is insufficient to address all the objectives of the present 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, IVF or 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	Parallel-group, randomised, controlled, single-centre trial Power calculation not reported Approved by the hospital's ethics committee No source of funding or conflict of interest reported
Participants	Country: Italy Setting: AGUNCO Obstetrics and Gynecology Centre, Rome Population: women referred to the centre from January 1998 until April 2005 for fertility problems were examined for inclusion in the study. All women underwent routine examinations including the study of ovarian function (follicle-stimulating hormone, luteinising hormone, estradiol and progesterone concentrations); prolactin, free triiodothyronine, free thyroxine and thyroid-stimulating hormone concentrations; post-coital test; transvaginal ultrasonography; hysterosalpingography; and analysis of the partner's semen. The transvaginal ultrasonography was performed in order to diagnose the presence of uterine fibroids. After these examinations all patients who were found to be affected by uterine fibroids excluding all other causes of infertility were asked to participate in the study Type of subfertility: all women had been suffering from infertility for at least 1 year (range: 1 to 5 years); no further clarification on primary versus secondary subfertility Mean age: the mean age in the patients with submucous fibroids alone was 31.4 ± 2.5 years; the mean age in the patients with mixed submucous-intramural fibroids was 32.2 ± 2.5 years N recruited = 193 women N participants = 181 women N participants with submucous fibroids only = 52 women N participants with mixed submucous-intramural fibroids = 42 women Inclusion criteria: age $\leq$ 35 years; infertility for at least 1 year; presence of one knot and/or fibroid of diameter $\leq$ 40 mm and absence of other causes of infertility at the performed examinations Exclusion criteria: presence of 2 or more knots and/or fibroids of diameter > 40 mm; body weight > 20% of normal weight; and use of medication containing oestrogens, progestins or androgens within 8 weeks prior to the study Duration of the study: 86 months; the study was conducted from January 1998 until April 2005
Interventions	2 interventions were compared: • The intervention group was treated with hysteroscopic surgery to remove the fibroids (n = 52) • The control group was not treated (n = 42) Patients were examined by transvaginal ultrasonography 3 months after surgery for control Patients 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). Patients who underwent surgery were suggested to abstain from

	having sexual intercourse for 3 months and then to start having regular fertility-oriented intercourse Patients were monitored for up to 12 months after study commencement
Outcomes	A clinical pregnancy was defined by the visualisation of an embryo with cardiac activity at 6 to 7 weeks of pregnancy Miscarriage was classified as clinical loss of an intrauterine pregnancy between the 7th and 12th weeks of gestation
Notes	The authors state that the differences in pregnancy rates between the comparison groups are statistically significant for the patients with submucous fibroids ($P < 0.05$), which is in contrast with the calculation of the results in RevMan The definition of knot is unclear: it could not be clarified since we failed to contact the study authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "*Subsequently, women of each group were randomized into two subgroups, according to a randomization table*" Comment: low risk of selection bias related to random sequence generation
Allocation concealment (selection bias)	Unclear risk	Method not stated: no further clarification obtained from the study authors Comment: unclear risk of selection bias related to allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This item was not assessed as justified in the protocol
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This item was not assessed as justified in the protocol
Incomplete outcome data (attrition bias) All outcomes	Low risk	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 in-*

		tramural-subserosal fibroids (IM-SS group)". Quote: "*Out of 181 women, 68 become pregnant*" Comment: low risk for attrition bias
Selective reporting (reporting bias)	Unclear risk	Quote from the abstract: "*The main outcome measures were the pregnancy rate and the miscarriage rate*". Quote from the results' section: "*Out of 181 women, 68 become pregnant. Pregnancy rates according to the location of the fibroids and the different treatments are reported in Table II. Among the 68 women who became pregnant, 25 had a miscarriage*". Comment: unclear risk for reporting bias. Although the main outcomes specified in the abstract were measured and reported in the results section, no study protocol could be obtained. The published report fails to include results for the live birth rate, which is 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	The mean ages and duration of infertility in the intervention and control group of women with submucous fibroids are not reported. No further clarification by the authors was obtained It is unclear whether there might have been imbalance in the baseline characteristics between the comparison groups

Pérez-Medina 2005

Methods	Parallel-group, randomised, controlled, single-centre trial A power analysis was 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 Approved by the hospital's ethics committee No source of funding or conflict of interest reported
Participants	Country: Spain Setting: infertility unit of an university tertiary hospital in the Spanish capital Madrid Population: women with unexplained, male or female factor infertility for at least 24 months bound to undergo intrauterine insemination with a sonographic diagnosis of endometrial polyps Unexplained infertility was diagnosed in patients with normal ovulatory cycles, semen analysis, HSG and postcoital testing. Male factor infertility was diagnosed if 2 semen analyses obtained at least 1 month apart were subnormal according to the WHO criteria. Female factor infertility was diagnosed in patients with ovulatory dysfunction, cervical factor or endometriosis Type of subfertility: primary subfertility (correspondence with the study authors) Mean age: treatment group = 30.8 years (26.7 to 34.9), control group = 30.9 years (26. 5 to 35.3) N recruited = 452 women N randomised = 215 women Inclusion criteria: women with at least 24 months of subfertility with a sonographic diagnosis of endometrial polyps bound to undergo intrauterine insemination for unexplained, male or female factor infertility Exclusion criteria: women > 39 years of age, anovulation, azoospermia, uncorrected tubal disease or previous unsuccessful use of recombinant FSH Duration of the study: 50 months; the study was conducted from January 2000 to February 2004
Interventions	One surgeon (the first author of the study TP-M) performed all hysteroscopic procedures by intention in an outpatient office setting under local anaesthesia 2 interventions were compared: • Hysteroscopic polypectomy using a 5.5 mm continuous flow office hysteroscope with a 1.5 mm scissors and forceps (n = 107) • Diagnostic hysteroscopy using a 5.5 mm continuous flow office hysteroscope and polyp biopsy (n = 108) Duration: women were scheduled to receive 4 cycles of IUI with subcutaneous injection of recombinant FSH 50 IU daily from the third day, and the first IUI was planned for 3 cycles after hysteroscopy in both groups. 4 IUI cycles were attempted before finishing the trial
Outcomes	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
Notes	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*" 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 patient was excluded from randomisation. The numbers of women undergoing a laparoscopy were balanced between the 2 comparison groups 2. In this study IUI was performed for various indications: male factor (21%), cervical factor (11%), endometriosis (11%), or unexplained subfertility (49%) and ovulation disorder (33%). Anovulation is 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 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 4. Data on the size of the polyps in the control group could not be obtained for similar reasons as 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	Unclear risk	This item was not assessed as justified in the protocol
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This item was not assessed as justified in the protocol
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: no intention-to-treat analysis; missing outcome data are balanced in numbers across the comparison groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	Unclear risk	Quote: "*Clinical pregnancy was the main outcome measure analysed to determine the effectiveness of treatment. We studied the crude pregnancy rate in both groups. The secondary outcomes were to compare the time for success in each group and to determine whether the size of the endometrial polyp influenced the pregnancy rate*". Comment: the study protocol is no longer available to the first study author since he no longer works in the tertiary university fertility centre and has moved to 4 different hospitals during the last 10 years. Although the published report includes results on all the outcomes specified in the methods section, it nevertheless fails to include results for the live birth rate, which is the primary outcome of interest that would be expected to have been reported 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

Pérez-Medina 2005 (*Continued*)

		clarification could be obtained for the lack of data on hysteroscopic complications
Other bias	Low risk	No evidence for imbalance in the baseline characteristics

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
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
Aghahosseini 2012	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing hysteroscopy prior to a subsequent IVF attempt versus immediate IVF without prior hysteroscopy conducted in patients with 2 or more failed IVF cycles with unsuspected or no uterine cavity abnormalities. Main outcomes: biochemical pregnancy, clinical pregnancy and delivery rates
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 versus the application of an intrauterine balloon without amnion graft as an adjunctive procedure after the hysteroscopic lysis of severe intrauterine adhesions, diagnosed at office hysteroscopy in women with infertility with or without menstrual disorders as the primary symptom. Outcomes assessed were improvement in adhesion grade, improvement in menstruation, increased uterine length at sounding, complications and reproductive outcome
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 versus the Versapoint device. Mixed population of women with septate uterus and a history of recurrent miscarriage or primary subfertility. Outcomes assessed were operative parameters, complications, need for a second intervention and reproductive outcome parameters

(*Continued*)

Darwish 2008	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing extended sectioning by resectoscopy versus sequential cold knife excision for treating a complete uterocervicovaginal septum in a mixed population of women suffering from infertility or pregnancy loss. Main outcome measures: operating time, perioperative bleeding, complications, reproductive outcome, and patient and husband satisfaction
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 versus surgical treatment alone in women aged 18 to 65 years, suffering from other gynaecological conditions than subfertility. Primary outcome: adhesion score at second look hysteroscopy
Demirol 2004	Not addressing the research questions described in the protocol Parallel-group randomised comparison between office hysteroscopy prior to a subsequent IVF attempt or immediate IVF without prior office hysteroscopy conducted in patients with 2 or more failed IVF cycles with unsuspected or no uterine cavity abnormalities. Outcome measures: number of oocytes retrieved, fertilisation rate, number of embryos transferred, first trimester miscarriage and clinical pregnancy rates
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 versus no adhesion barrier after hysteroscopic synechiolysis in a mixed population of women suffering from infertility or other gynaecological conditions. Primary outcome: incidence of de novo intrauterine adhesions, adhesion scores, patency of the internal uterine ostium
El-Nashar 2011	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing diagnostic hysteroscopy with directed biopsy and/or hysteroscopic treatment of unsuspected uterine cavity abnormalities versus no hysteroscopy in women with primary infertility treated with ICSI. Primary outcome: clinical pregnancy
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 versus 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
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 versus 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
Muzii 2007	Not addressing the research questions described in the protocol Parallel-group randomised trial in women aged 18 to 75 years comparing operative hysteroscopy using the monopolar resectoscope versus hysteroscopic bipolar electrode excision for the treatment of endometrial polyps. Outcomes: operating times, difficulty of the operation, surgeon satisfaction with the procedure,

(*Continued*)

	complications, postoperative pain and patient satisfaction
Pabuccu 2008	Quasi-randomised trial comparing early second look office hysteroscopic adhesiolysis after hysteroscopic adhesiolysis and IUD insertion versus no early second look operative hysteroscopy in subfertile women with intrauterine adhesions. The method of sequence generation is based on alternation: women were allocated 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 versus metroplasty with preservation of the cervical septum. Outcome measures: operating time, distending media deficit, total distending media used, intraoperative bleeding, complications and reproductive outcome
Rama Raju 2006	Not addressing the research questions described in the protocol Parallel-group randomised trial conducted in patients with 2 or more failed IVF cycles with unsuspected or no uterine cavity abnormalities comparing office 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
Shawki 2010	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 office hysteroscopy in patients before ICSI treatment compared to ICSI without prior hysteroscopy. Main outcomes were the incidence of unsuspected uterine abnormalities and implantation and clinical pregnancy rates
Shokeir 2010	Published report describing a parallel-group randomised trial comparing hysteroscopic myomectomy versus diagnostic hysteroscopy and biopsy in women with otherwise unexplained primary infertility and submucous fibroids. Primary outcome: clinical pregnancy rates Quote from Fertility and Sterility 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 Hum. Reprod., 20 (2005) 1632-1635, DOI:10.1093/humrep/deh822".*
Tonguc 2008	Not addressing the research questions described in the protocol Parallel-group randomised comparing hysteroscopic lysis of intrauterine adhesions with or without adjunctive therapy (cyclical hormone replacement therapy alone or intrauterine device alone or both co-treatments combined) after hysteroscopic metroplasty in a mixed population of women with subfertility and/or recurrent miscarriage. Main outcomes: incidence of de novo adhesion formation and ongoing pregnancy rate
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 versus hysteroscopic morcellation in a mixed population of women suffering from infertility or other gynaecological conditions. Outcome measures: 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 versus micro scissors for treating uterine septum in women with repeated miscarriage. Outcome measures: mean operating time, mean

(*Continued*)

	amount of distension medium used and complications

ICSI: intracytoplasmic sperm injection
IUD: intrauterine device
IVF: in vitro fertilisation
SIS: saline infusion sonography
TVUS: transvaginal ultrasound

Characteristics of studies awaiting assessment *[ordered by study ID]*

Pansky 2009

Methods	Single-centre, prospective, single-blind randomised controlled pilot study
Participants	30 women aged 18 to 50 years with retained products of conception
Interventions	Application of Oxiplex/AP gel after hysteroscopic treatment versus no gel after hysteroscopic treatment
Outcomes	Primary: safety of intrauterine application of Oxiplex/AP gel defined by immediate and late adverse effects at 18 months such as fever, intrauterine adhesion formation and changes in menstrual pattern Secondary: efficacy of intrauterine application of Oxiplex/AP gel in reducing adhesion formation following hysteroscopic treatment for retained products of conception
Notes	Current status on 1 November 2012: study completed; we contacted the first author - no response at present

Trninić -Pjević 2011

Methods	Clinical controlled trial - not clear whether random sequence generation was used
Participants	This study included 480 women under 38, who had undergone IVF or IVF/ICSI - embryo transfer cycles, in which one or more good quality embryos were transferred
Interventions	Hysteroscopy versus no hysteroscopy
Outcomes	Clinical pregnancy
Notes	Current status on 1 November 2012: no further clarification by the first author at present

ICSI: intracytoplasmic sperm injection
IVF: in vitro fertilisation

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

Broekmans 2010

Trial name or title	SIGnificance of Routine Hysteroscopy Prior to a First 'in Vitro Fertilization' (IVF) Treatment Cycle - inSIGHT ClinicalTrials.gov NCT01242852
Methods	Multicentre, single-blind, parallel-group randomised controlled trial
Participants	Women with primary or secondary infertility due to undergo IVF treatment with normal transvaginal ultrasound in the follicular phase of the menstrual cycle
Interventions	Office hysteroscopy combined with a saline infusion sonography prior to a first IVF cycle compared to starting IVF without prior hysteroscopy
Outcomes	Primary: ongoing pregnancy Secondary: costs, implantation rate, miscarriage rate and patient tolerance
Starting date	Current status on 1 November 2012: recruiting
Contact information	F.J. Broekmans, M.D., PhD University Medical Center Utrecht, Utrecht the Netherlands 3584CX Telephone: +31 887551041 e-mail: F.J.Broekmans@Umcutrecht.nl
Notes	

El-Khayat 2012

Trial name or title	Does office hysteroscopy and endometrial snip improve IUI outcome?: a randomized controlled trial
Methods	Allocation: randomised; endpoint classification: efficacy study; intervention model: parallel assignment; masking: single-blind (participant); primary purpose: treatment
Participants	Inclusion criteria: 18 to 38 years old, at least 1 patent tube, unexplained infertility or anovulation or mild to moderate male factor infertility, previous failed IUI Exclusion criteria: indication for ICSI
Interventions	Control group: office hysteroscopy Intervention group: office hysteroscopy and endometrial snip
Outcomes	Primary outcome: clinical pregnancy rate at 10 months Secondary outcome: ongoing pregnancy rate at 12 months
Starting date	Current status on 1 November 2012: recruiting since February 2012
Contact information	Waleed El-Khayat, MD Faculty of Medicine, Cairo University Telephone: 23655215 e-mail: Waleed_Elkhart@yahoo.com

El-Khayat 2012 (*Continued*)

Notes	

El-Toukhy 2009

Trial name or title	TRial of OutPatient HYsteroscopy in in-vitro fertilisation (IVF)- Trophy in IVF ISRCTN35859078
Methods	Multicentre, parallel-group randomised controlled trial
Participants	Women 36 years of age or less, undergoing IVF or ICSI with 2 to 4 previous failed fresh embryo transfers and no submucous or intramural uterine fibroids distorting the uterine cavity or untreated tubal hydrosalpinges
Interventions	Outpatient hysteroscopy in the follicular phase of the menstrual cycle where the IVF cycle is due to start, followed by standard IVF treatment compared to IVF treatment without a prior outpatient hysteroscopy
Outcomes	Primary: live birth event per cycle started, measured after 9 months of embryo transfer Secondary: embryo implantation rate, pregnancy rate per cycle, clinical pregnancy rate per cycle, miscarriage rate per pregnancy achieved, measured 2 and 4 weeks after embryo transfer
Starting date	Current status on 1 November 2012: trial completed; trial results are being processed at present
Contact information	Dr Tarek El-Toukhy Assisted Conception Unit 11th Floor, Tower Wing Guy's Hospital Great Maze Pond, London, United Kingdom Telephone: +44 (0)20 7188 0497; Fax: +44 (0)20 7188 0490 e-mail: Tarek.El-Toukhy@gstt.nhs.uk
Notes	

Maramazi 2012

Trial name or title	Effect of hysteroscopy before intra uterine insemination on fertility in infertile couples patients referred to Imam Khomeini Hospital, Ahwaz IVF
Methods	Randomisation: randomised; blinding: not blinded; placebo: not used; assignment: parallel
Participants	Infertile patients aged 20 to 40 years who are candidates for IUI with normal hysterosalpingography Exclusion criterion: ovarian hyperstimulation syndrome in patients suffering complications during surgery and hysteroscopy
Interventions	Intervention group: hysteroscopy Control group: no hysteroscopy
Outcomes	Primary outcome: pregnancy, diagnosed by ultrasound at 2 months after intervention Secondary outcome: complications of hysteroscopy and treatment side effects of ovulation induction

Maramazi 2012 (*Continued*)

Starting date	Current status on 1 November 2012: completed; the first author was contacted
Contact information	Dr. Farideh Maramazi Imam Khomeini Hospital - IVF Department Jundi Shapur University of Medical Sciences, Ahwaz Telephone: 00986112222114 e-mail: maramazi.f@ajums.ac.ir
Notes	

Revel 2011

Trial name or title	Safety study of use of hyaluronic acid gel to prevent intrauterine adhesions in hysteroscopic surgery
Methods	Single-centre, parallel-group, randomised, single-blind controlled trial
Participants	Women 18 years of age or older, undergoing hysteroscopic treatment
Interventions	Application of hyaluronic acid gel (study group); the control intervention is not described
Outcomes	Patient satisfaction following gel application at 2 months
Starting date	Current status on 1 November 2012: not yet recruiting
Contact information	Ariel Revel, MD Hadassah Medical Organization Telephone: 97226777111 ext 76389 e-mail: ariel2@hadassah.org.il
Notes	

Sohrabvand 2012

Trial name or title	Evaluation of diagnostic hysteroscopy findings in patients candidate for ART (IVF, ICSI) and its effect on pregnancy rate compared to control group
Methods	Randomisation: randomised; blinding: not blinded; placebo: not used; assignment: parallel; purpose: treatment
Participants	Inclusion criteria: hysterosalpingography normal during the past 12 months; normal vaginal ultrasound; age between 25 and 40 years; absence of abnormal uterine bleeding and no hysteroscopy performed in the last 6 months
Interventions	Control group: hysteroscopy is not done In the intervention group a hysteroscopy is performed; submucosal myoma or polyps 1 cm or larger cervical or uterine adhesions will be resolved

Sohrabvand 2012 (*Continued*)

Outcomes	Primary outcomes: presence of pathology Secondary outcomes: pregnancy 14 days after embryo transfer
Starting date	Current status on 1 November 2012: recruiting since June 2012
Contact information	Farnaz Sohrabvand Vali-e-Asr Reproductive Health & Research Center Telephone: 00982166939320 e-mail: fsohrabvand@yahoo.com
Notes	

ICSI: intracytoplasmic sperm injection
IUI: intrauterine insemination
IVF: in vitro fertilisation

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 regular fertility-oriented intercourse	1	52	Odds Ratio (M-H, Fixed, 95% CI)	2.04 [0.62, 6.66]
1.2 Removal of mixed submucous-intramural fibroids vs regular fertility-oriented intercourse	1	42	Odds Ratio (M-H, Fixed, 95% CI)	3.24 [0.72, 14.57]
2 Miscarriage	1	94	Odds Ratio (M-H, Fixed, 95% CI)	1.54 [0.47, 5.00]
2.1 Removal of submucous fibroids only vs regular fertility-oriented intercourse	1	52	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.27, 5.97]
2.2 Removal of mixed submucous-intramural fibroids vs regular fertility-oriented intercourse	1	42	Odds Ratio (M-H, Fixed, 95% CI)	2.0 [0.32, 12.33]

Comparison 2. Operative hysteroscopy versus control in women undergoing MAR 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 IUI	1	204	Odds Ratio (M-H, Fixed, 95% CI)	4.41 [2.45, 7.96]

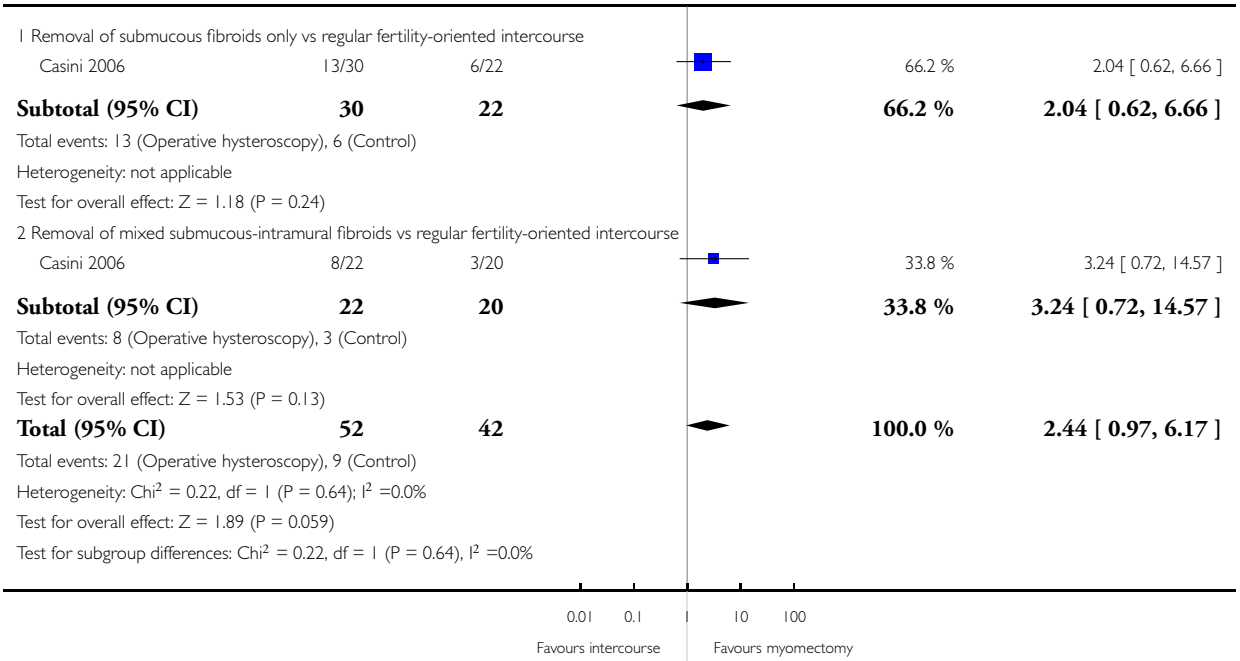
Analysis 1.1. Comparison 1 Operative hysteroscopy versus control in women with otherwise unexplained subfertility and suspected major uterine cavity abnormalities, Outcome 1 Clinical pregnancy.

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

Study or subgroup	Operative hys-teroscopy n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Removal of submucous fibroids only vs regular fertility-oriented intercourse					
Casini 2006	13/30	6/22		66.2 %	2.04 [0.62, 6.66]
Subtotal (95% CI)	**30**	**22**		**66.2 %**	**2.04 [0.62, 6.66]**
Total events: 13 (Operative hysteroscopy), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.18 (P = 0.24)					
2 Removal of mixed submucous-intramural fibroids vs regular fertility-oriented intercourse					
Casini 2006	8/22	3/20		33.8 %	3.24 [0.72, 14.57]
Subtotal (95% CI)	**22**	**20**		**33.8 %**	**3.24 [0.72, 14.57]**
Total events: 8 (Operative hysteroscopy), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.53 (P = 0.13)					
Total (95% CI)	**52**	**42**		**100.0 %**	**2.44 [0.97, 6.17]**
Total events: 21 (Operative hysteroscopy), 9 (Control)					
Heterogeneity: Chi^2 = 0.22, df = 1 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 1.89 (P = 0.059)					
Test for subgroup differences: Chi^2 = 0.22, df = 1 (P = 0.64), I^2 =0.0%					



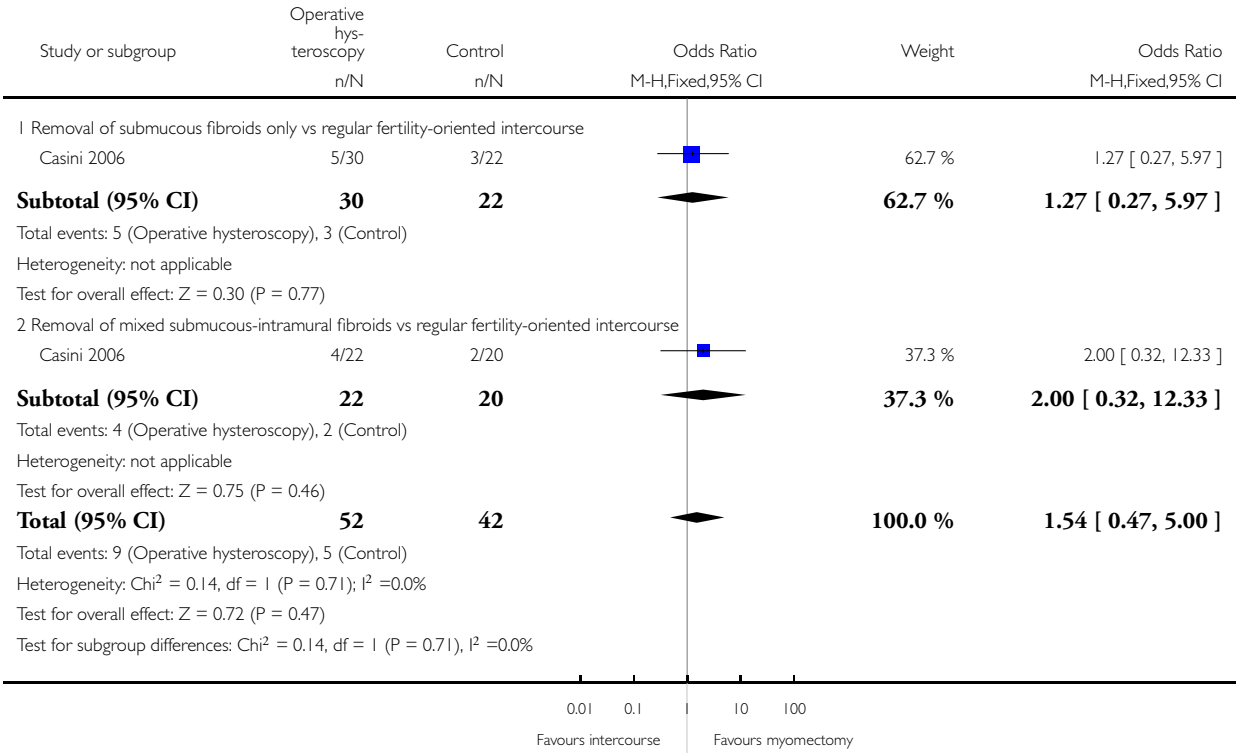
Analysis 1.2. Comparison 1 Operative hysteroscopy versus control in women with otherwise unexplained subfertility and suspected major uterine cavity abnormalities, Outcome 2 Miscarriage.

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 Miscarriage

Study or subgroup	Operative hys-teroscopy n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Removal of submucous fibroids only vs regular fertility-oriented intercourse					
Casini 2006	5/30	3/22		62.7 %	1.27 [0.27, 5.97]
Subtotal (95% CI)	**30**	**22**		**62.7 %**	**1.27 [0.27, 5.97]**
Total events: 5 (Operative hysteroscopy), 3 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.30 (P = 0.77)					
2 Removal of mixed submucous-intramural fibroids vs regular fertility-oriented intercourse					
Casini 2006	4/22	2/20		37.3 %	2.00 [0.32, 12.33]
Subtotal (95% CI)	**22**	**20**		**37.3 %**	**2.00 [0.32, 12.33]**
Total events: 4 (Operative hysteroscopy), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.75 (P = 0.46)					
Total (95% CI)	**52**	**42**		**100.0 %**	**1.54 [0.47, 5.00]**
Total events: 9 (Operative hysteroscopy), 5 (Control)					
Heterogeneity: Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 0.72 (P = 0.47)					
Test for subgroup differences: Chi^2 = 0.14, df = 1 (P = 0.71), I^2 =0.0%					

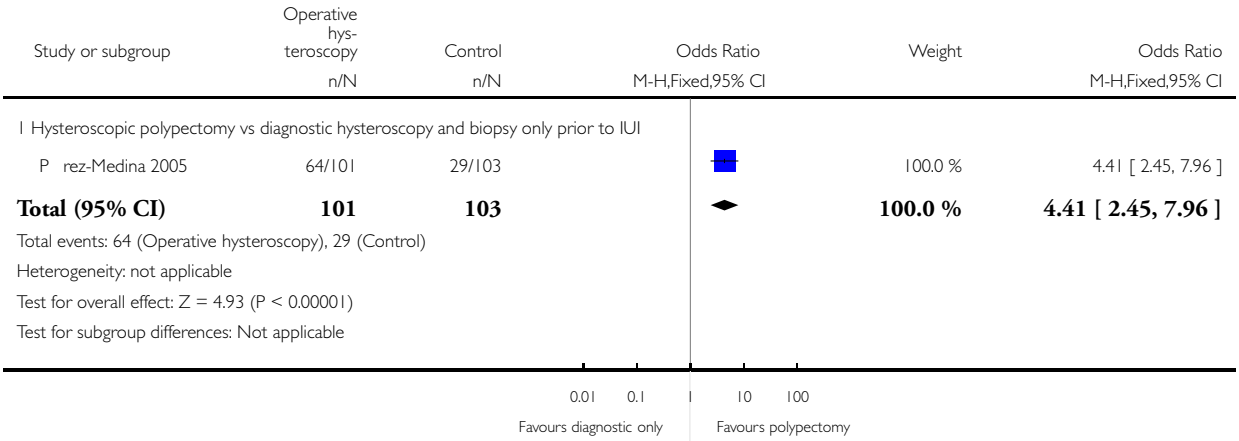


Analysis 2.1. Comparison 2 Operative hysteroscopy versus control in women undergoing MAR with suspected major uterine cavity abnormalities, Outcome 1 Clinical pregnancy.

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

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

Outcome: 1 Clinical pregnancy



ADDITIONAL TABLES

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

Polyp size	Clinical pregnancy[1]	Clinical pregnancy rate (95% CI)[2]
< 5 mm	19/25	76% (from 72% to 80%)
5 to 10 mm	18/32	56% (from 53% to 59%)
11 to 20 mm	16/26	61% (from 58% to 65%)
> 20 mm	11/18	61% (from 58% to 64%)

[1] Clinical pregnancy is defined by a pregnancy diagnosed by ultrasound visualisation of at least one gestational sac per woman randomised.

[2] No 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[1])						
1	RCT	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[4]
Miscarriage (follow-up 1 year; ultrasound[5])						
1	RCT	Serious[2]	No serious inconsistency	No serious indirectness	Serious[3]	Reporting bias[4]

[1] A clinical pregnancy was defined by the visualisation of an embryo with cardiac activity at six to seven weeks' gestational age.
[2] Unclear allocation concealment.
[3] Wide confidence intervals.
[4] Unclear selective reporting and unclear whether there is other bias caused by imbalance in the baseline characteristics.
[5] Miscarriage was defined by the clinical loss of an intrauterine pregnancy between the 7^{th} and 12^{th} weeks of gestation.

Table 3. GRADE evidence profile - endometrial polyps prior to IUI

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[1])						
1	RCT	No serious limitations	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2] Strong association[3]

[1] Clinical pregnancy was defined by the presence of at least one gestational sac on ultrasound.
2 There was some potential for reporting bias.
3 Large treatment effect in the absence of plausible confounders.

APPENDICES

Appendix 1. CENTRAL search strategy

1 exp Hysteroscopy/ (236)
2 Hysteroscop$.tw. (403)
3 Uteroscop$.tw. (0)
4 endoscop$.tw. (8356)
5 Endoscopy/ (1145)
6 or/1-5 (9009)
7 exp Infertility/ (1486)
8 subfertil$.tw. (128)
9 Infertilit$.tw. (1311)
10 exp Sperm Injections, Intracytoplasmic/ or exp Reproductive Techniques/ or exp Reproductive Techniques, Assisted/ or exp Fertilization in Vitro/ (2521)
11 (IVF or ICSI).tw. (2158)
12 artificial insemination.tw. (53)
13 assisted conception.tw. (56)
14 exp Myoma/ or exp Leiomyoma/ (353)
15 (myoma or myomectomy).tw. (273)
16 septate uterus.tw. (9)
17 polypectomy.tw. (128)
18 adhesiolysis.tw. (47)
19 exp Tissue Adhesions/ (224)
20 (remov$ adj2 adhesion).tw. (4)
21 polyp$.tw. (2523)
22 uterine septa.tw. (7)
23 uterine septum.tw. (9)
24 synechiotomy.tw. (1)
25 Leiomyoma$.tw. (190)
26 uterine malformation$.tw. (6)
27 (Uter$ adj4 Neoplasm$).tw. (1)
28 (uter$ adj4 abnormalit$).tw. (43)
29 fibroid$.tw. (210)
30 or/7-29 (7836)
31 6 and 30 (460)
32 limit 31 to yr="2011 -Current" (22)
Database: Cochrane Central Register of Controlled Trials (CENTRAL) July 2012.

Appendix 2. Cochrane Menstrual Disorders and Subfertility Group Specialised Register search strategy

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 " embryo transfer" or "zygote intrafallopian transfer" 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"
155 records
Most recent update 6 August 2012.

Appendix 3. MEDLINE through PubMed search strategy

("Hysteroscopy"[MeSH] OR Uterine Endoscop*[All Fields] OR Uteroscop*[All Fields] OR Hysteroscopic Surg*[All Fields] OR (hysteroscopic[All Fields] AND (polypectom*[All Fields] OR polyp removal*[All Fields] OR myomectom*[All Fields] OR synechiolysis[All Fields] OR synechiotomy[All Fields] OR adhesiolysis[All Fields] OR metroplast*[All Fields] OR septoplast*[All Fields] OR septum resection*[All Fields]))) AND (Subfertility[tiab] OR "Infertility, Female"[MeSH] OR (female[tiab] AND (Infertility[tiab] OR Sterility[tiab]))) AND ((("Endometrium"[MeSH] OR Endometri*[All Fields]) AND (polyp[All Fields] OR polyps[All Fields])) OR "Leiomyoma"[MeSH] OR Leiomyoma[All Fields] OR Leiomyomas[All Fields] OR Fibromyoma[All Fields] OR Fibromyomas[All Fields] OR Fibroid[All Fields] OR Fibroids[All Fields] OR fibromas[All Fields] OR Myoma[All Fields] OR Myomas[All Fields] OR ((Synechiae[All Fields] AND ((Intrauterine[All Fields] OR uterine[All Fields]) AND adhesion*)) OR "Asherman Syndrome"[All Fields] OR "Asherman's Syndrome"[All Fields] OR "Ashermans Syndrome"[All Fields] OR ((septa[All Fields] OR septum[All Fields]) AND (uterine[All Fields] OR intrauterine[All Fields])) OR "Uterine Diseases"[MeSH] OR "Uterine Neoplasms"[MeSH] OR ((uterine[All Fields] OR intrauterine[All Fields]) AND "Congenital Abnormalities"[MeSH]) OR "Fertilization in Vitro"[MeSH] OR (Fertilization[All Fields] AND "in Vitro"[All Fields]) OR IVF[All Fields] OR ICSI[All Fields] OR "Reproductive Techniques"[MeSH] OR "Embryo Transfer"[MeSH] OR "Zygote Intrafallopian Transfer"[MeSH] OR "Insemination, Artificial"[MeSH] OR ((intrauterine OR artificial) AND insemination[All Fields]))) AND (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh])
#1 ("Hysteroscopy"[MeSH] OR Uterine Endoscop*[All Fields] OR Uteroscop*[All Fields] OR Hysteroscopic Surg*[All Fields] OR (hysteroscopic[All Fields] AND (polypectom*[All Fields] OR polyp removal*[All Fields] OR myomectom*[All Fields] OR synechiolysis[All Fields] OR synechiotomy[All Fields] OR adhesiolysis[All Fields] OR metroplast*[All Fields] OR septoplast*[All Fields] OR septum resection*[All Fields]))) (3493)

#2 (Subfertility[tiab] OR "Infertility, Female"[MeSH] OR (female[tiab] AND (Infertility[tiab] OR Sterility[tiab]))) (27267)

#3 ((("Endometrium"[MeSH] OR Endometri*[All Fields]) AND (polyp[All Fields] OR polyps[All Fields])) OR "Leiomyoma"[MeSH] OR Leiomyoma[All Fields] OR Leiomyomas[All Fields] OR Fibromyoma[All Fields] OR Fibromyomas[All Fields] OR Fibroid[All Fields] OR Fibroids[All Fields] OR fibromas[All Fields] OR Myoma[All Fields] OR Myomas[All Fields] OR ((Synechiae[All Fields] AND ((Intrauterine[All Fields] OR uterine[All Fields]) AND adhesion*)) OR "Asherman Syndrome"[All Fields] OR "Asherman's Syndrome"[All Fields] OR "Ashermans Syndrome"[All Fields] OR ((septa[All Fields] OR septum[All Fields]) AND (uterine[All Fields] OR intrauterine[All Fields])) OR "Uterine Diseases"[MeSH] OR "Uterine Neoplasms"[MeSH] OR ((uterine[All Fields] OR intrauterine[All Fields]) AND "Congenital Abnormalities"[MeSH]) OR "Fertilization in Vitro"[MeSH] OR (Fertilization[All Fields] AND "in Vitro"[All Fields]) OR IVF[All Fields] OR ICSI[All Fields] OR "Reproductive Techniques"[MeSH] OR "Embryo Transfer"[MeSH] OR "Zygote Intrafallopian Transfer"[MeSH] OR "Insemination, Artificial"[MeSH] OR ((intrauterine OR artificial) AND insemination[All Fields]))) (278308)

#4 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT humans[mh]) (2621133)
#5 1 AND 2 AND 3 AND 4 (69)
Most recent update: 27 October 2012.

Appendix 4. EMBASE through Embase.com search strategy

'hysteroscopy'/exp OR 'hysteroscopy' OR ('uterine' OR 'uterine'/exp OR uterine AND endoscop* AND [embase]/lim) OR (uteroscop* AND [embase]/lim) OR (hysteroscopic NEAR/1 surg* AND [embase]/lim) OR ('myomectomy'/exp OR 'myomectomy' OR (myomectom* AND [embase]/lim) OR (polypectom* AND [embase]/lim) OR ('polyp'/exp OR polyp AND removal) OR (synechiolysis AND [embase]/lim) OR synechiotomy OR (adhesiolysis AND [embase]/lim) OR (metroplasty AND [embase]/lim) OR (septoplast* AND [embase]/lim) OR (septum NEAR/1 resection* AND [embase]/lim) AND hysteroscopic AND [embase]/lim) AND ('female infertility'/exp OR 'female infertility' OR (female:ab,ti AND (infertility:ab,ti OR sterility:ab,ti) AND [embase]/lim) OR (female:ab,ti AND (subfertility:ab,ti OR sterility:ab,ti) AND [embase]/lim)) AND (endometri* NEAR/1 polyp* AND [embase]/lim OR ('endometrium'/exp OR 'endometrium' AND polyp* AND [embase]/lim) OR 'leiomyoma'/exp OR 'leiomyoma' OR (leiomyoma* AND [embase]/lim) OR (fibromyoma* AND [embase]/lim) OR (fibroid* AND [embase]/lim) OR (fibroma* AND [embase]/lim) OR (myoma* AND [embase]/lim) OR (synechiae AND (intrauterine OR uterine) NEAR/1 adhesion* AND [embase]/lim) OR 'uterus synechia'/exp OR 'uterus synechia' OR ('asherman syndrome'/exp OR 'asherman syndrome' OR 'ashermans syndrome' AND [embase]/lim) OR (asher-

man* AND ('syndrome' OR 'syndrome'/exp OR syndrome) AND [embase]/lim) OR ('septa' OR 'septa'/exp OR septa OR septum AND ('uterine' OR 'uterine'/exp OR uterine OR 'intrauterine' OR 'intrauterine'/exp OR intrauterine) AND [embase]/lim) OR 'uterine diseases'/exp OR 'uterine diseases' OR 'uterine neoplasms'/exp OR 'uterine neoplasms' OR 'congenital uterus malformation'/exp OR 'congenital uterus malformation' OR 'fertilization in vitro'/exp OR 'fertilization in vitro' OR ('fertilization' OR 'fertilization'/exp OR fertilization AND ('in vitro'/exp OR 'in vitro') OR ivf AND [embase]/lim) OR 'icsi' OR 'icsi'/exp OR icsi OR 'reproductive techniques assisted'/exp OR 'reproductive techniques assisted' OR 'embryo transfer'/exp OR 'embryo transfer' OR ('zygote' OR 'zygote'/exp OR zygote AND intrafallopian AND transfer) OR 'artificial insemination'/exp OR 'artificial insemination' OR ((intrauterine OR artificial) NEAR/1 insemination AND [embase]/lim)) AND ('clinical trial'/exp OR 'clinical trial' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'randomization'/exp OR 'randomization' OR 'single blind procedure'/exp OR 'single blind procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'crossover procedure'/exp OR 'crossover procedure' OR 'placebo'/exp OR 'placebo' OR (randomi?ed AND controlled AND trial* AND [embase]/lim) OR (rct AND [embase]/lim) OR ('random allocation'/exp OR 'random allocation' AND [embase]/lim) OR ('randomly allocated' AND [embase]/lim) OR ('allocated randomly' AND [embase]/lim) OR (allocated NEAR/2 random AND [embase]/lim) OR ('single blind$' AND [embase]/lim) OR ('double blind$' AND [embase]/lim) OR ((treble OR triple) NEAR/2 blind$ AND [embase]/lim) OR (placebo$ AND [embase]/lim) OR 'prospective study'/exp OR 'prospective study') NOT ('case study'/exp OR 'case study' OR 'case report'/exp OR 'case report' OR 'abstract report'/exp OR 'abstract report' OR 'letter'/exp OR 'letter') NOT ('animal'/exp OR 'animal' NOT ('human'/exp OR 'human'))
1 'hysteroscopy'/exp OR 'hysteroscopy' (7410)
2 'uterine' OR 'uterine'/exp OR uterine AND endoscop* AND [embase]/lim (20736)
3 uteroscop* AND [embase]/lim (18)
4 hysteroscopic NEAR/1 surg* AND [embase]/lim (319)
5 'myomectomy'/exp OR 'myomectomy' (3643)
6 myomectom* AND [embase]/lim (3252)
7 polypectom* AND [embase]/lim (6659)
8 'polyp'/exp OR polyp AND removal (1924)
9 synechiolysis AND [embase]/lim (50)
10 synechiotomy (7)
11 adhesiolysis AND [embase]/lim (1138)
12 metroplasty AND [embase]/lim (337)
13 septoplast* AND [embase]/lim (919)
14 septum NEAR/1 resection* AND [embase]/lim (75)
15 OR/ 5-14 (13953)
16 hysteroscopic AND [embase]/lim (2720)
17 15 AND 16 (777)
18 1 OR 2 OR 3 OR 4 OR 17 (23782)
19 'female infertility'/exp OR 'female infertility'(34316)
20 female:ab,ti AND (infertility:ab,ti OR sterility:ab,ti) AND [embase]/lim (5400)
21 female:ab,ti AND (subfertility:ab,ti OR sterility:ab,ti) AND [embase]/lim (1321)
22 19 OR 20 OR 21 (37525)
23 endometri* NEAR/1 polyp* AND [embase]/lim (1969)
24 'endometrium'/exp OR 'endometrium' (72576)
25 polyp* AND [embase]/lim (337581)
26 24 AND 25 (3631)
27 23 OR 26 (3770)
28 'leiomyoma'/exp OR 'leiomyoma' (16602)
29 leiomyoma* AND [embase]/lim(11724)
30 28 OR 29 (18992)
31 fibromyoma* AND [embase]/lim (250)
32 fibroid* AND [embase]/lim (4397)
33 fibroma* AND [embase]/lim (10749)
34 myoma* AND [embase]/lim (10547)
35 synechiae AND (intrauterine OR uterine) NEAR/1 adhesion* AND [embase]/lim (28)
36 'uterus synechia'/exp OR 'uterus synechia' (736)
37 'asherman syndrome'/exp OR 'asherman syndrome' OR 'ashermans syndrome' AND [embase]/lim (741)

38 asherman* AND ('syndrome' OR 'syndrome'/exp OR syndrome) AND [embase]/lim (205)
39 'septa' OR 'septa'/exp OR septa OR septum AND ('uterine' OR 'uterine'/exp OR uterine OR 'intrauterine' OR 'intrauterine'/exp OR intrauterine) AND [embase]/lim (1398)
40 'uterine diseases'/exp OR 'uterine diseases' (177248)
41 'uterine neoplasms'/exp OR 'uterine neoplasms' (98381)
42 'congenital uterus malformation'/exp OR 'congenital uterus malformation' (3598)
43 'fertilization in vitro'/exp OR 'fertilization in vitro' (35590)
44 'fertilization' OR 'fertilization'/exp OR fertilization AND ('in vitro'/exp OR 'in vitro') OR ivf AND [embase]/lim (46128)
45 'icsi' OR 'icsi'/exp OR icsi (12561)
46 'reproductive techniques assisted'/exp OR 'reproductive techniques assisted' (71428)
47 'embryo transfer'/exp OR 'embryo transfer' (20233)
48 'zygote'/exp OR zygote AND intrafallopian AND transfer (135)
49 'artificial insemination'/exp OR 'artificial insemination' (13789)
50 (intrauterine OR artificial) NEAR/1 insemination AND [embase]/lim (8647)
51 27 OR 30-50 (277312)
52 18 AND 22 AND 51 (1335)
53 'clinical trial'/exp OR 'clinical trial' (1051671)
54 'randomized controlled trial'/exp OR 'randomized controlled trial' (354684)
55 'randomization'/exp OR 'randomization' (71847)
56 'single blind procedure'/exp OR 'single blind procedure' (15974)
57 'double blind procedure'/exp OR 'double blind procedure' (111202)
58 'crossover procedure'/exp OR 'crossover procedure' (35533)
59 'placebo'/exp OR 'placebo' (297437)
60 randomi?ed AND controlled AND trial* AND [embase]/lim (319263)
61 rct AND [embase]/lim (10028)
62 'random allocation'/exp OR 'random allocation' AND [embase]/lim (34639)
63 'randomly allocated' AND [embase]/lim (14933)
64 'allocated randomly' AND [embase]/lim (1585)
65 allocated NEAR/2 random AND [embase]/lim (683)
66 'single blind$' AND [embase]/lim (17490)
67 'double blind$' AND [embase]/lim (145208)
68 (treble OR triple) NEAR/2 blind$ AND [embase]/lim (261)
69 placebo$ AND [embase]/lim (267409)
70 'prospective study'/exp OR 'prospective study' (263707)
71 OR/ 53-70 (1447482)
72 'case study'/exp OR 'case study' (67892)
73 'case report'/exp OR 'case report' AND [embase]/lim (1307072)
74 'abstract report'/exp OR 'abstract report' (89566)
75 'letter'/exp OR 'letter'(855918)
76 OR/ 72-75 (2186940)
77 71 NOT 76 (1388842)
78 'animal'/exp OR 'animal' (18459336)
79 'human'/exp OR 'human' (17532043)
80 78 NOT 79 (2128576)
81 77 NOT 80 (1358768)
82 52 AND 81 (248)

Most recent update 27 October 2012.

Appendix 5. CINAHL through EBSCOHOST search strategy

S1 TX hysteroscopy (345)
S2 TX uterine endoscop* (4)
S3 TX uteroscop* (0)
S4 TX hysteroscopic surg* (24)
S5 TX hysteroscopic polypectom* (4)
S6 "hysteroscopic polyp removal*" (16) Smart Text searching
S7 TX hysteroscopic myomectom* (11)
S8 TX hysteroscopic adhesiolys* (2)
S9 TX hysteroscopic synechiolys* (0)
S10 TX hysteroscopic synechiotomy (0) Smart Text searching
S11 TX hysteroscopic metroplast* (5)
S12 TX hysteroscopic septoplast* (0) Smart Text searching
S13 TX hysteroscopic septum resection (24) Smart Text searching
S14 TX hysteroscopic sept* resection (1)
S15 TX subfertility (259)
S16 TX infertility (4418)
S17 TX sterility (328)
S18 TX female (667400)
S19 TX endometri* polyp* (69)
S20 TX leiomyoma* (1078)
S21 TX fibromyoma* (5)
S22 TX fibroid* (512)
S23 TX fibroma* (343)
S24 TX myoma* (147)
S25 TX "synechia*" (67)
S26 TX intrauterine adhesion* (8)
S27 TX uterine adhesion* (15)
S28 TX Asherman* syndrome (7)
S29 TX uterine sept* (12)
S30 TX intrauterine sept* (6)
S31 TX "septate uterus" (15)
S32 TX uterine diseases (367)
S33 TX uterine neoplasm* (863)
S34 TX uterine congenital abnormalit* (1)
S35 TX uterine congenital abnormalities (1)
S36 TX uterine malformation* (21)
S37 TX in vitro fertilisation (187)
S38 TX in vitro fertilization (1821)
S39 TX IVF (690)
S40 TX assisted reprod* (768)
S41 TX ICSI (128)
S42 TX embryo transfer(402)
S43 TX zygote intrafallopian transfer (8)
S44 TX artificial insemination (300)
S45 TX intrauterine insemination (80)
S46 TX IUI (40)
S47 (MH "Clinical Trials") (75886)
S48 PT clinical trial* (51716)
S49 (MH "Randomized Controlled Trials") (11719)
S50 PT randomized controlled trial* (11680)
S51 "randomised controlled trial" (3920)

S52 PT randomised controlled trial* (198)
S53 (MH "Random Assignment") (28382)
S54 TX Randomi*ation (3032)
S55 TX single blind* (6185)
S56 TX double blind* (532573)
S57 TX triple blind* (93)
S58 TX treble blind* (0) Smart Text searching
S59 TX Placebo* (23319)
S60 TX prospective stud* (145823)
S61 OR/S47-60 (729472)
S62 OR/S1-14 (359)
S63 OR/S15-17 (4864)
S64 S18 AND S63 (3060)
S65 0R/S19-46 (5398)
S66 S61 and S62 and S64 and S65 (9)

Most recent update: 28 October 2012.

Appendix 6. ISI Web of Science search strategy

TS=((((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)))))
60 records time span = all years. Databases = SCI-EXPANDED, CPCI-S.
Most recent update 27 October 2012.

Appendix 7. Items of data extraction

1. Source

1. Study ID
2. Report Id
3. Review author ID
4. Citation and contact details

2. Eligibility

1. Confirm eligibility for review
2. Reason for exclusion

3. Trial characteristics

1.Study design

- Random sequence generation
- Patient recruitment
- Patient in- and exclusion criteria
- Allocation concealment

- Completeness of outcome data
- Selective outcome reporting
- Other potential sources of bias

2. Follow-up
   - Duration of follow-up
   - Type of follow-up

3. 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

4. Study setting
   - Single-centre or multicentre
   - Location
   - Timing and duration

5. Diagnostic criteria
   - Screening by TVS
   - Screening by HSG
   - Screening by TVS and HSG
   - Screening by other ultrasound diagnostic procedures, e.g. SIS or GIS
   - Screening by hysteroscopy
   - Diagnosis confirmed by hysteroscopy and biopsy

4. Characteristics of the study participants

1. Baseline characteristics
   - Age
   - Primary or secondary subfertility
   - Duration of subfertility
   - Diagnostic work-up: baseline FSH, semen analysis, diagnosis of tubal pathology, confirmatory test of ovulation
   - Other contributory causes to subfertility than uterine factor
   - Previous treatments - IVF, IUI or other treatments

2. Treatment characteristics
   - IUI natural cycle
   - IUI controlled ovarian stimulation with anti-oestrogens or gonadotropins
   - IVF protocol and number of embryos transferred
   - ICSI protocol and number of embryos transferred
   - detailed description of the hysteroscopic procedure

5. Interventions

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

For each intervention and comparison group of interest:

- Specific intervention
- Intervention details
- Timing of the intervention

6. Outcomes

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

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

- Live birth delivery rate
- Hysteroscopy complication rate

Secondary outcome:

- Ongoing pregnancy rate
- Clinical pregnancy with fetal heart beat
- Clinical pregnancy rate
- Miscarriage rate

For each outcome of interest:

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

7. Miscellaneous

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

CONTRIBUTIONS OF AUTHORS

JB co-ordinated the writing of the protocol and review.

JK co-authored the protocol for the background section and searched the literature.

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

SW independently extracted study data.

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

DECLARATIONS OF INTEREST

FB and JK (principal investigator) and BWM (co-investigator) are at present involved in the 'inSIGHT trial' (SIGnificance of Routine Hysteroscopy Prior to a First 'in Vitro Fertilization' Treatment Cycle: NCT 01242852), which is financially supported by ZonMw, a Dutch government operated consortium responsible for granting funds in the field of clinical practice research. This study is at present in the recruitment phase.

SOURCES OF SUPPORT

Internal sources

- CEBAM, Belgium.

Research grant was obtained through CEBAM, the Centre for Evidence-based Medicine, Belgian Branch of the Cochrane Collaboration

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. 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.

2. A 'Summary of findings' table using the GRADE approach has been added.

3. 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.

4. In the Assessment of heterogeneity section of the review we have added the Q-statistic.

5. 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.