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 (8 September 2014), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2014, Issue 9), MEDLINE (1950 to 12 October 2014), EMBASE (inception to 12 October 2014), CINAHL (inception to 11 October 2014) and other electronic sources of trials including trial registers, sources of unpublished literature and reference lists.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 2013 to October 2014) 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 review authors independently assessed studies for inclusion and risk of bias, and extracted data. We contacted study authors for additional information.

Main results

We retrieved 12 randomised trials possibly addressing the research questions. Only two studies (309 women) met the inclusion criteria. Neither reported the primary outcomes of live birth or procedure related complications. In women with otherwise unexplained subfertility and submucous fibroids there was no conclusive evidence of a difference between the intervention group treated with hysteroscopic myomectomy and the control group having regular fertility-oriented intercourse during 12 months for the outcome of clinical pregnancy. A large clinical benefit with hysteroscopic myomectomy cannot be excluded: if 21% of women with fibroids achieve a clinical pregnancy having timed intercourse only, the evidence suggests that 39% of women (95% CI 21% to 58%) will achieve a successful outcome following the hysteroscopic removal of the fibroids (odds ratio (OR) 2.44, 95% confidence interval (CI) 0.97 to 6.17, P = 0.06, 94 women, *very low quality evidence*). There is no evidence of a difference between the comparison groups for the outcome of miscarriage (OR 0.58, 95% CI 0.12 to 2.85, P = 0.50, 30 clinical pregnancies in 94 women, *very low quality evidence*). The hysteroscopic removal of polyps prior to IUI can increase the chance of a clinical pregnancy compared to simple diagnostic hysteroscopy and polyp biopsy: if 28% of women achieve a clinical pregnancy with a simple diagnostic hysteroscopy, the evidence suggests that 63% of women (95% CI 50% to 76%) will achieve a clinical pregnancy after the hysteroscopic removal of the endometrial polyps (OR 4.41, 95% CI 2.45 to 7.96, P < 0.00001, 204 women, *moderate quality evidence*).

Authors' conclusions

A large benefit with the hysteroscopic removal of submucous fibroids for improving the chance of clinical pregnancy in women with otherwise unexplained subfertility cannot be excluded. The hysteroscopic removal of endometrial polyps suspected on ultrasound in women prior to IUI may 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

Review question

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

Background

Human life starts when a fertilised egg has successfully implanted in the inner layer of the cavity of the womb. It is believed that abnormalities originating from this site, such as polyps, fibroids, septa or adhesions, may disturb this important event. The removal of these abnormalities by doing a hysteroscopy using a very small diameter inspecting device might therefore increase the chance of becoming pregnant either spontaneously or after specialised fertility treatment, such as insemination or in vitro fertilisation.

Study characteristics

We found only two studies in 309 women. The first study compared the removal of fibroids versus no removal in 94 women wishing to become pregnant from January 1998 until April 2005. The second study compared the removal of polyps versus simple hysteroscopy only in 215 women before insemination with husband's sperm from January 2000 to February 2004. The evidence is current to September 2014. No study reported funding sources.

Key results

None of the studies reported live birth.

The study on the removal of fibroids in women with unexplained infertility suggests does not exclude a higher chance of conceiving after surgery compared to regular sexual intercourse for 12 months. However uncertainty remains because the number of women (94) and the number of pregnancies (30) are too small for any differences between both comparison groups to reach statistical significance.

If 21% of women with fibroids achieve a pregnancy having timed intercourse only, the evidence suggests that between 21% to 58% of women will achieve a successful outcome following the hysteroscopic removal of the fibroids.

The second study on the hysteroscopic removal of polyps supports a benefit with the hysteroscopic removal of polyps. If 28% of women become pregnant in the control group, the evidence suggests that between 50% to 76% of women will become pregnant after the removal of the endometrial polyps

No study reported data on adverse procedure related events.

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

Quality of the evidence

The quality of the evidence on fibroids is very low: there was only one poorly conducted study lacking sufficient data.

The quality of the evidence on polyps is moderate: there were issues with selective reporting of outcomes.

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				
Live birth	No data were reported for this primary outcome.					
Hysteroscopy complications	No data were reported for this primary outcome.					
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 0.58** (0.12 to 2.8)	30 pregnancies in 94 women (1 study)	⊕◯◯◯ **very low**[2,3,4]	
	556 per 1000	**421 per 1000** (131 to 778)				

*The basis for the **assumed risk** is the control group risk of the single included study (Casini 2006). The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio

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

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

Major uterine cavity abnormalities can be found in 10% to 15% of women seeking treatment for subfertility; they usually consist of the presence of excessive normal uterine tissue (Wallach 1972). The most common acquired uterine cavity abnormality is an endometrial polyp. This benign, endometrial stalk-like mass protrudes into the uterine cavity and has its own vascular supply. Depending on the population under study and the applied diagnostic test, endometrial polyps can be found in 1% to 41% of the subfertile population (Silberstein 2006). A fibroid is an excessive growth originating from the muscular part of the uterine cavity. Fibroids are present in 2.4% of subfertile women without any other obvious cause of subfertility (Donnez 2002). A submucous fibroid is located underneath the endometrium and is thought to interfere with fertility by deforming the uterine cavity. Intrauterine adhesions are fibrous tissue strings connecting parts of the uterine wall. They are commonly caused by inflammation or iatrogenic tissue damage (meaning involuntarily caused by a physician's intervention, for example an aspiration curettage after miscarriage) and are present in 0.3% to 14% of subfertile women (Fatemi 2010). A septate uterus is a congenital malformation in which the longitudinal band separating the left and right Müllerian ducts, which form the uterus in the human female fetus, has not been entirely resorbed. A uterine septum is present in 1% to 3.6% of women with otherwise unexplained subfertility (Saravelos 2008).

Ultrasonography (US), preferably transvaginally (TVS), is used to screen for possible endometrium or uterine cavity abnormalities in the work-up of subfertile women. This evaluation can be expanded with hysterosalpingography (HSG), saline infusion/gel instillation sonography (SIS/GIS) and diagnostic hysteroscopy. Diagnostic hysteroscopy is generally considered as 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 intended for evaluating the uterine cavity only, it is called a diagnostic hysteroscopy. If the observed pathology requires further treatment, the procedure is called an operative hysteroscopy. In everyday practice, a diagnostic hysteroscopy confirming the presence of pathology will be followed by an operative hysteroscopy in a symptomatic 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 (surgical instruments used to divide and remove tissue during endoscopic surgery) and aspiration cannulae, or unipolar or bipolar electrodiathermy instruments.

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

For endometrial polyps, submucous fibroids, intrauterine adhesions and uterine septum, observational studies have shown a clear improvement in the spontaneous pregnancy rate after the hysteroscopic removal of the abnormality (Taylor 2008). 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 may negatively affect the uterine environment, and therefore the likelihood of conceiving (Rogers 1986), it has been recommended that these abnormalities be diagnosed and treated by hysteroscopy to improve the cost-effectiveness in subfertile women undergoing MAR, where recurrent implantation failure is inevitably associated with a higher economic burden to society.

The study of the association between subfertility and major uterine cavity abnormalities might increase our current understanding of the complex mechanisms of human embryo implantation. This could lead to the development of cost-effective strategies in reproductive medicine with benefits for both the individual woman 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 main clinical problem, other gynaecological complaints, such as pain or bleeding, might or might not be present.
- Women of reproductive age with subfertility, undergoing IUI, IVF or ICSI with endometrial polyps, submucous fibroids, septate uterus or intrauterine adhesions detected by US, SIS, GIS, HSG, diagnostic hysteroscopy or any combination of these methods.

Exclusion criteria

- Women of reproductive age with 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 400 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. The 'Summary of findings' table was generated

using GRADEpro software (GRADE profiler version 3.6). This table evaluates 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).
GRADE profiler version 3.6: See: https://tech.cochrane.org/revman/other-resources/gradepro/download.

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 review authors (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 were merged and duplicates removed using specialised software (EndNote Web 3.5 - last done on 14 October 2014).
EndNote Web: See: http://www.myendnoteweb.com/EndNoteWeb.html.

Electronic searches

We searched the following bibliographic databases, trial registers and web sites: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2014, Issue 9) (Appendix 1), the Menstrual Disorders and Subfertility Group (MDSG) Specialised Register (8 September 2014) (Appendix 2), MEDLINE using PubMed (1950 to 12 October 2014) (Appendix 3) and EMBASE using EMBASE.com (inception to 12 October 2014) (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* 2014, Issue 9 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 12 October 2014) (www.crd.york.ac.uk).
- National Guideline Clearinghouse (www.guideline.gov) for evidence-based guidelines (from inception to 12 October 2014).
- 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 11 October 2014) (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 12 October 2014).
- Citation indexes: Science Citation Index through Web of Science (http://scientific.thomson.com/products/sci/) - SCI-EXPANDED (1955 to 11 October 2014) and Conference Proceedings Citation Index - Science (CPCI-S) (1990 to 11 October 2014) and Scopus available at the Biomedical Library Gasthuisberg of the Catholic University of Leuven) (from inception to 12 October 2014).
- Conference abstracts and proceedings on the ISI Web of Knowledge (http://isiwebofknowledge.com) applying 'SCI-EXPANDED' (1955 to 11 October 2014) and 'CPCI-S' (1990 to 11 October 2014) (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 11 October 2014).
- European grey literature through Open Grey database (from inception to 11 October 2014) (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 11 October 2014).

Searching other resources

Two review authors (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 January 2013 to 12 October 2014) 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 review authors 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) 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 review authors, one methodologist (JB) and one topic area specialist (SW), independently assessed the studies that appeared to meet the inclusion criteria by using data extraction forms based on the items listed in the protocol of this Cochrane review (Appendix 7). We pilot-tested the data extraction form and process by reviewing 10 randomly chosen study reports. In the pilot phase one retracted record (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. We assessed all 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 to report 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 except miscarriage were expressed as per woman randomised; miscarriage was expressed as per pregnancy. 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 Review Manager 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

Review author JB entered the data and carried out the statistical analysis of the data using Review Manager 5 software. We considered the outcomes live birth and pregnancy to be positive and higher numbers as a benefit. We considered the outcomes miscarriage and hysteroscopy complications in the protocol as negative effects and higher numbers harmful. These aspects were taken into consideration when assessing the summary graphs. In the quantitative synthesis an increase in the odds of a particular outcome,

either beneficial or harmful, was displayed graphically to the right of the centre-line and a decrease in the odds of an outcome to the left of the centre-line.

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

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

We planned to define analyses that were both comprehensive and mutually exclusive so that all eligible study results were slotted into one of the two predefined strata only. If 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 modifier 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 aimed to perform sensitivity analyses for the primary outcomes to determine whether the conclusions are robust to arbitrary decisions made regarding the eligibility and analysis. These analyses included consideration of whether conclusions would have differed if:

- eligibility 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

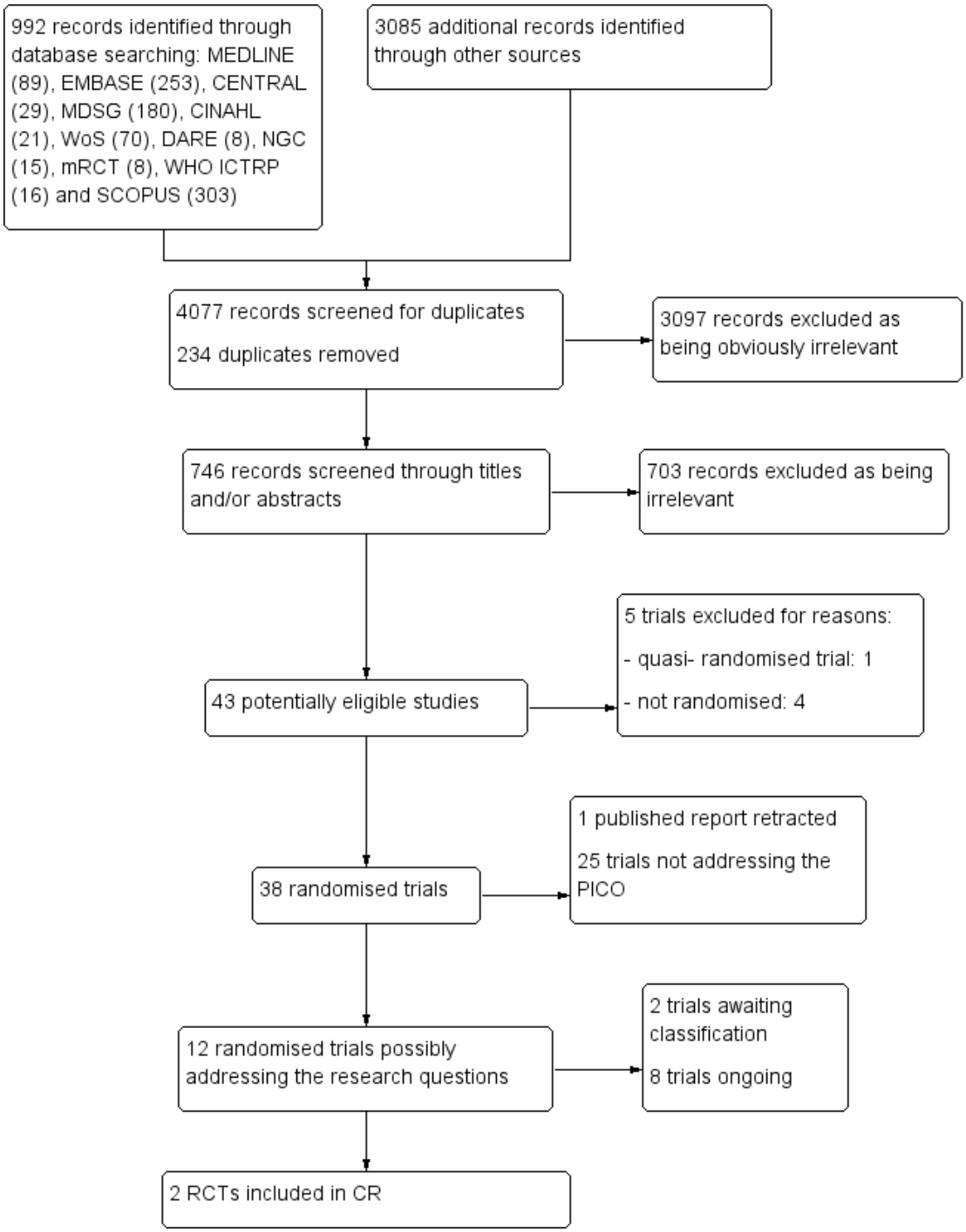
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

Review authors JB and JK scanned the titles and abstracts of the results of the search strings. There were 29 records from CENTRAL, 180 records from the MDSG Specialised Register, 89 from MEDLINE, 253 from EMBASE and 70 from Web of Science. An electronic search in DARE produced eight records; there were 15 guidelines from National Guideline Clearinghouse, eight records from the metaRegister of controlled trials and 16 records from WHO ICTRP. We identified 303 additional references in Scopus. We identified 21 records in CINAHL. No records were retrieved in LILACS and Open Grey. We handsearched 3085 abstracts in the proceedings of the American Society for Reproductive Medicine; no additional abstracts were identified after contacting the experts of the European Society for Gynaecological Endoscopy (ESGE). After combining 992 records identified from electronic searches with 3085 additional records through searching other sources, we screened 4077 records for duplicates by using a specialised software program (EndNote Web). After the removal of 234 duplicate references and 3097 records that were obviously irrelevant we retrieved 43 potentially eligible studies. We excluded five studies for being quasi- or not randomised (Characteristics of excluded studies). We excluded one study (Shokeir 2010) because the study report had been retracted at the request of the publisher. Another 25 studies were not included in the present Cochrane review for not addressing the research questions (Characteristics of excluded studies). We retrieved 12 possibly relevant studies: two RCTs are awaiting classification (Characteristics of studies awaiting classification) and eight are still ongoing (Characteristics

of ongoing studies). We finally included two RCTs addressing the research questions of this Cochrane review (Characteristics of included 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 with or without intramural 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, hysterosalpingography (HSG) and postcoital testing. Female factor infertility was diagnosed in women with ovulatory dysfunction, cervical factor or endometriosis. Male factor infertility was diagnosed if two semen analyses obtained at least one month apart were subnormal according to the WHO criteria. The sonographic diagnosis of endometrial polyps was established by the demonstration of the vascular stalk of the endometrial polyp by colour Doppler in a hyperechogenic formation with regular contours occupying the uterine cavity, surrounded by a small hypoechogenic halo. Women older than 39 years of age or with anovulation or uncorrected tubal disease or previous unsuccessful use of recombinant follicle stimulating hormone (FSH), as well as women with a male partner with azoospermia, were excluded from randomisation.

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 intrauterine insemination (IUI), using subcutaneous injections of FSH 50 IU (international units) daily from the third day of the cycle.The first IUI treatment cycle was started three cycles after the operative hysteroscopy. In the control group, the endometrial polyps suspected on Doppler 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 in the control group were scheduled to receive four cycles of IUI, using subcutaneous injections of FSH 50 IU daily from the third day of the cycle. The first IUI treatment cycle was scheduled three cycles after the diagnostic hysteroscopy. Four IUI cycles were attempted before finishing the trial.

Outcomes

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

The first trial (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 31 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; four trials (De Angelis 2010; Gao 2013; Mohammed 2014; Trninić -Pjević 2011) are non-randomised studies. We excluded 25 trials because they did not address the pre-specified PICO (**P**articipants, **I**nterventions, **C**omparisons and **O**utcomes) research questions of this Cochrane review. Eight trials (Aghahosseini 2012; Demirol 2004; El-Nashar 2011; Elsetohy 2015; El-Toukhy 2009; Fatemi 2007; Rama Raju 2006; Shawki 2010) studied the effectiveness of hysteroscopy in subfertile women bound to undergo in vitro fertilisation (IVF) or intracytoplasmic sperm injection (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. Nine trials (Abu Rafea 2013; Acunzo 2003; Amer 2010; De Iaco 2003; Di Spiezio Sardo 2011; Guida 2004; Lin 2014; Pansky 2009; Tonguc 2008) studied the effectiveness of adjunctive therapies (hyaluronic acid gel, amnion graft, balloon catheter, cyclical hormone replacement therapy alone or intrauterine device alone or both co-treatments combined) for the prevention of intrauterine adhesions following hysteroscopic adhesiolysis. Four trials (Colacurci 2007; Darwish 2008; Parsanezhad 2006; Youssef 2013) 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 (Clark 2014; Moramezi 2012).

See the table Characteristics of studies awaiting classification.

Ongoing studies

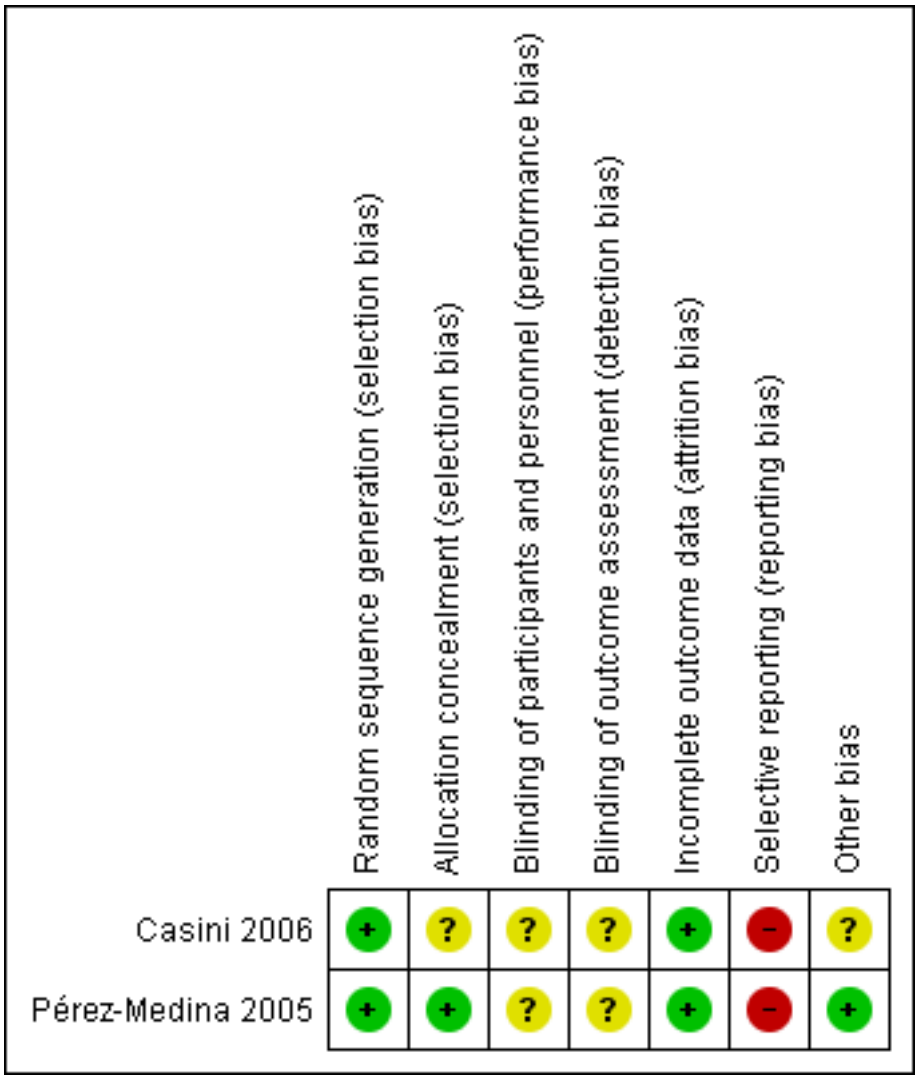
Eight trials are ongoing (Abiri 2014; Basma 2013; Broekmans 2010; El-Khayat 2012; Hare 2013; Revel 2011; Sohrabvand 2012; Weiss 2005).

See the table Characteristics of ongoing studies.

Risk of bias in included studies

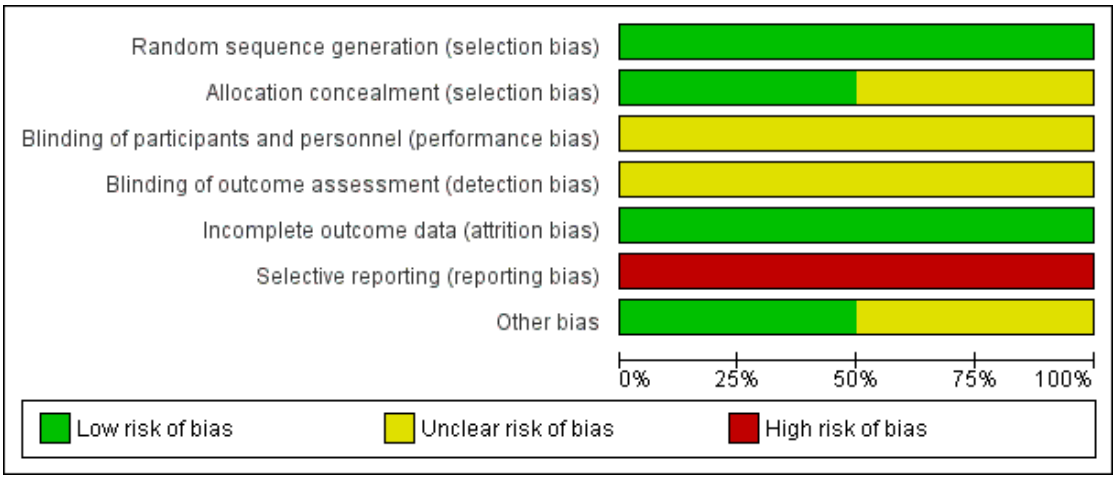
See the 'Risk of bias' summary for the review authors' judgements about each risk of bias item in the included study (Figure 2).

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 method used was not reported and no further clarification by the authors could be obtained.

Blinding

Originally we intended not to assess the 'Risk of bias' items 'blinding of participants and personnel' and 'blinding of outcome assessors' for either of the two included studies as pre-specified-and justified- in the published protocol for this review (see Bosteels 2011). The editorial reviewers insisted on assessing all six 'Risk of bias' items as stated in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We judged both studies (Casini 2006; Pérez-Medina 2005) to be at unclear risk of performance and detection bias since in both studies the methods for blinding participants, personnel and outcome assessors were not stated and no further clarification could be obtained.

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 high risk of reporting bias. 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. Although a plausible explanation was given by the contact author of one study (Pérez-Medina 2005), we judged that it could have been possible to obtain data on the live birth rates if the study authors had contacted the referring gynaecologists (see Characteristics of included studies). 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 this might have caused imbalance in the baseline characteristics between the comparison groups in this randomised trial (Casini 2006). Moreover it is unclear whether hysteroscopy had been performed in all participants to confirm the position of the ultrasonically detected fibroids.

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** Operative hysteroscopy compared with control for unexplained subfertility associated with suspected major uterine cavity abnormalities; **Summary of findings 2** Operative hysteroscopy compared with control for suspected major uterine cavity abnormalities prior to medically assisted reproduction

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

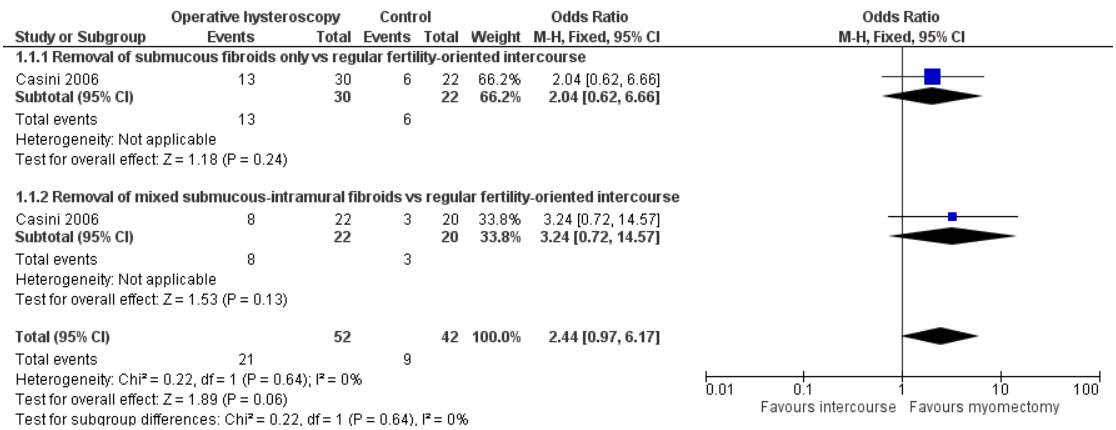
There were no data for this primary outcome.

Secondary outcomes

1.3. Clinical pregnancy

In women with otherwise unexplained subfertility for at least one year and one submucous fibroid of diameter ≤ 40 mm, an important benefit with the removal of the fibroid by hysteroscopy compared to regular fertility-oriented intercourse cannot be ruled out for the secondary outcome of clinical pregnancy: there is no conclusive evidence for statistically significant differences between both comparison groups (odds ratio (OR) 2.44, 95% confidence interval (CI) 0.97 to 6.17, P = 0.06, one randomised controlled trial (RCT), 94 women) (Analysis 1.1; Figure 4).

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 per woman randomised.

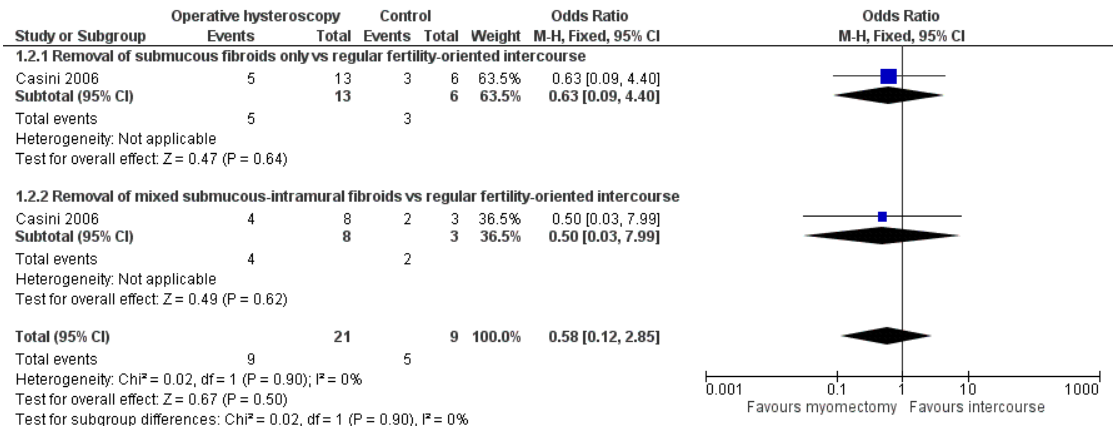


We pre-specified in the protocol (Bosteels 2011) that a minimally important clinical difference (MICD) of 5% for the live birth rate would be considered as being relevant for the benefits of the intervention. The data for the one secondary outcome studied indicate a clinically important difference of 18% (95% CI 0% to 37%, P = 0.05) between the two comparison groups. This is a post hoc analysis.

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 per clinical pregnancy (OR 0.58, 95% CI 0.12 to 2.85, P = 0.50, one RCT, 30 clinical pregnancies in 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 per clinical pregnancy.



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 conclusive evidence for statistically significant differences between both comparison groups for the secondary outcome clinical pregnancy in the 'submucous only' subgroup (OR 2.04, 95% CI 0.62 to 6.66, P = 0.24, one RCT, 52 women), or the 'mixed submucous-intramural' subgroup (OR 3.24, 95% CI 0.72 to 14.57, P = 0.13, one RCT, 42 women); the tests for subgroup differences demonstrated no statistical heterogeneity beyond chance (Chi^2 = 0.22, df = 1 (P = 0.64), I^2 = 0%). There is no conclusive evidence for statistically

significant differences between both comparison groups for the secondary outcome miscarriage in the 'submucous only' subgroup (OR 0.63, 95% CI 0.09 to 4.40, P = 0.64, one RCT, 19 clinical pregnancies in 52 women) or the 'mixed submucous-intramural' subgroup (OR 0.50, 95% CI 0.03 to 7.99, P = 0.62, one RCT, 11 clinical pregnancies in 42 women); the tests for subgroup differences demonstrated no statistical heterogeneity beyond chance (Chi^2 = 0.02, df = 1 (P = 0.90), I^2 = 0%).

Uterine septum

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

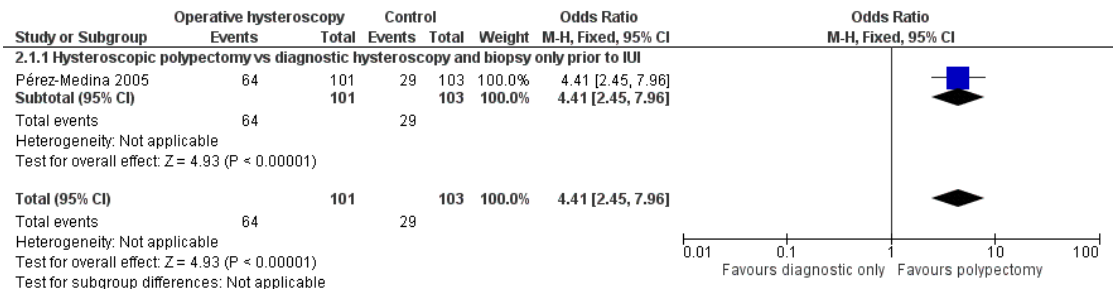
There were no data for this primary outcome.

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 4.41, 95% CI 2.45 to 7.96, 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 per woman randomised.



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

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) or intracytoplasmic sperm injection (ICSI)

No studies were retrieved.

Submucous fibroids prior to IUI, IVF or ICSI

No studies were retrieved.

Uterine septum prior to IUI, IVF or ICSI

No studies were retrieved.

Intrauterine adhesions prior to IUI, IVF or 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				
Live birth	No data were reported for this primary outcome.					
Hysteroscopy complications	No data were reported for this primary outcome.					
Clinical pregnancy ultrasound[1] *4IUIcycles*	**Low-risk population**[2]		**OR 4.41** (2.45 to 7.96)	204 (1 study)	⊕⊕⊕◯ **moderate**[5]	
	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)				
Miscarriage	No data were reported for this secondary outcome.					

*The basis for the **assumed risk** in the low-, medium- or high-risk populations is the control group risk of three studies provided in the footnotes below. 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 high risk for selective outcome reporting.

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 intrauterine insemination (IUI), in vitro fertilisation (IVF) or 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. An important benefit with the removal of submucous fibroids by hysteroscopy in women with otherwise unexplained subfertility compared to expectant management cannot be excluded for the secondary outcome of clinical pregnancy. The lack of conclusive evidence for statistically significant differences between both comparison groups may be due to a type II error: we calculated that a sample size of 91 participants is needed to detect a difference of 19% for the outcome of clinical pregnancy between both comparison groups with a statistical power of 80% at a confidence level of 95% (α = 0.05 and ß = 0.20). In other words, a study population of at least 182 participants is needed to detect any statistically significant difference if present; compared to only 94 women in the single included study (Casini 2006). 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 comparison 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). A sensitivity analysis on the choice to use an intention-to-treat analysis by making the imputation that clinical pregnancies would not have occurred in participants with missing data rather than an 'available data' analysis did not demonstrate an impact on the overall results. 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 based on one single moderate quality trial. 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.

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

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 with the hysteroscopic removal of fibroids. It is generally accepted that submucous fibroids are very likely to interfere with normal fertility (Pritts 2001; Pritts 2009). In everyday practice most skilled hysteroscopic surgeons will counsel women with submucous fibroids associated with otherwise unexplained subfertility or bound to be treated with IUI, IVF or ICSI to have the submucous fibroids removed before further expectant management or MAR; besides offering participation in a pragmatic RCT on this topic there just seems no other sound clinical alternative.

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 an ovulatory disorder other than anovulation. In everyday clinical practice ovulatory disorder is by itself not an indication for IUI as opposed to male factor (Bensdorp 2007) and unexplained subfertility (Veltman-Verhulst 2012). We have considered doing a sensitivity analysis to 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 many: there is uncertainty about allocation concealment and it is unclear whether there was imbalance in the baseline characteristics of the study groups. There is a high risk of selective outcome reporting. 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 'moderate': there was a high risk of selective outcome reporting (see Assessment of risk of bias in included studies). 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 have carried 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

We briefly discuss the findings of 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 (risk ratio (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 reproductive outcome. These findings are not in accordance with the findings of a Cochrane review on the surgical treatment of fibroids for subfertility (Metwally 2012): according to these authors a large benefit favouring hysteroscopic myomectomy cannot be excluded, which is consistent with the findings of the present Cochrane review.

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. Finally, in a recent Cochrane review (Jayaprakasan 2014), the need for additional well-designed RCTs on the effectiveness of hysteroscopic polypectomy for improving reproductive outcome in subfertile women was stressed, which is in accordance with our findings.

AUTHORS' CONCLUSIONS

Implications for practice

A large benefit with hysteroscopic myomectomy in women with otherwise unexplained subfertility cannot be excluded. There was no conclusive evidence for statistically significant differences in clinical pregnancy rates between the comparison groups in the single published randomised trial.The quality of the evidence provided by this small single-centre study was graded as very low.

There may be a benefit with hysteroscopic polypectomy for improving the chance of conceiving in subfertile women with a sonographic diagnosis of endometrial polyps prior to intrauterine insemination for unexplained, male or female factor infertility for at least 24 months. We graded the quality of evidence provided by this single study as moderate.

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 (FSH, luteinising hormone, estradiol and progesterone concentrations); prolactin, free triiodothyronine, free thyroxine and thyroid-stimulating hormone concentrations; post-coital test; TVUS; hysterosalpingography; and analysis of the partner's semen. The TVUS 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	Two 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 TVUS 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

Casini 2006 (*Continued*)

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 It is not clear whether a hysteroscopy was done in all women to confirm the exact position of the ultrasonically detected fibroids

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 randomisation 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	Method not stated: no further clarification obtained from the study authors Comment: unclear risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not stated: no further clarification obtained from the study authors Comment: unclear risk of detection bias
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 intramural-subserosal fibroids (IM-SS group)".*

Casini 2006 (*Continued*)

		Quote: "*Out of 181 women, 68 become pregnant*" Comment: low risk for attrition bias
Selective reporting (reporting bias)	High risk	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 Failure to do a hysteroscopy in all women to confirm the position of the ultrasonically detected fibroids could have caused information bias

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 Two 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 footnote 3

Pérez-Medina 2005 (*Continued*)

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	Method not stated: no further clarification obtained from the study authors Comment: unclear risk of performance bias
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Method not stated: no further clarification obtained from the study authors Comment: unclear risk of detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: *"11 patients were lost from the study, 6 in the study group (3 lost to follow-up, 2 pathologic reports of submucosal myoma and 1 in whom the polyp was not confirmed) and 5 in the control group (1 lost to follow-up, 2 in whom the polyp was not confirmed and 2 pathologic reports of myoma)"* Comment: missing outcome data are balanced in numbers across the comparison groups, with similar reasons for missing data across groups
Selective reporting (reporting bias)	High risk	Although the published report includes results on all the outcomes specified in the methods section, it nevertheless fails to in-

		clude 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 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
Abu Rafea 2013	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing intrauterine balloon stenting versus no stenting following hysteroscopic treatment for septate uterus
Acunzo 2003	Not addressing the research questions described in the protocol Parallel-group randomised trial studying the efficacy of hyaluronic acid gel in preventing the development of intrauterine adhesions following hysteroscopic adhesiolysis. Mixed population of women with intrauterine adhesions, presenting with subfertility or other gynaecological complaints. Primary outcome: adhesion scores
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

(*Continued*)

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 two 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
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 utero-cervicovaginal 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 Angelis 2010	Study on the effectiveness of hysteroscopic metroplasty for small septate uterus in women with repeated IVF implantation failure. Although denoted by the authors as the first prospective randomised controlled study on this subject, the trial did not use a valid random sequence generation Quote: "These patients, once informed about the situation, were randomly allocated, depending on their personal decision ..."
De Iaco 2003	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing the application of hyaluronan derivative gel (Hyalobarrier® gel) after hysteroscopic surgery 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

(*Continued*)

	infertility treated with ICSI. Primary outcome: clinical pregnancy
El-Toukhy 2009	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing hysteroscopy versus no hysteroscopy in women with recurrent implantation failure with IVF.Status: completed
Elsetohy 2015	Not addressing the research questions described in the protocol Parallel-group randomised trial aimed at assessing the role of using the office hysteroscopy as a routine investigation in improving ICSI pregnancy rates in two groups of infertile women with no abnormality detected on transvaginal ultrasonographic examination
Fatemi 2007	Not addressing the PICO research question of this Cochrane review
Gao 2013	Observational non-randomised study on the effectiveness of hysteroscopy in women with repeated implantation failure
Guida 2004	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing hysteroscopic surgery for the removal of polyps, fibroids or septa followed by the application of auto-cross linked hyaluronic acid gel 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
Lin 2014	Not addressing the research questions described in the protocol Randomised trial comparing the efficacy of intrauterine balloon and intrauterine contraceptive device in the prevention of adhesion reformation following hysteroscopic adhesiolysis
Mohammed 2014	Comparative non-randomised study on the value of hysteroscopy prior to IVF/ICSI
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, 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.

(*Continued*)

Pansky 2009	Not addressing the research questions described in the protocol Parallel-group randomised trial studying the effectiveness of an anti-adhesion barrier gel in women treated by operative hysteroscopy for retained products of conception. Status:completed
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
Trninić -Pjević 2011	Clinical controlled trial on the effectiveness of hysteroscopy prior to IVF; no random sequence generation
van Dongen 2008	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing the hysteroscopic removal of polyps or fibroids by conventional hysteroscopy using a resectoscope 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 amount of distension medium used and complications

(*Continued*)

Youssef 2013	Not addressing the research questions described in the protocol Parallel-group randomised trial comparing 2 different surgical techniques for metroplasty: resectoscopy with monopolar knife versus small-diameter hysteroscopy fitted with a 5 Fr reusable bipolar electrode.Outcomes measures included pregnancy, miscarriage and live birth rates

ICSI: intracytoplasmic sperm injection
IUD: intrauterine device
IVF: in vitro fertilisation
PICO: Participants, **I**nterventions, Comparisons and Outcomes
SIS: saline infusion sonography
TVUS: transvaginal ultrasound

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

Clark 2014

Methods	Randomised controlled multi-centre equivalence trial
Participants	Abnormal uterine bleeding associated with a benign polyp. Inclusion criteria: 1. Abnormal uterine bleeding requiring diagnostic micro-hysteroscopy 2. Finding of a benign polyp (glandulocystic or pedunculated/grade 0 fibroid) on diagnostic micro-hysteroscopy 3. No hysteroscopic features suspicious of malignancy 4. Need for polypectomy Exclusion criteria: 1. Hysteroscopic features suggesting malignant lesion 2. Additional pathology necessitating hysterectomy
Interventions	Outpatient polypectomy will be performed immediately following diagnosis at outpatient hysteroscopy in most instances, although some participants may have their outpatient treatment scheduled to a later date, depending upon local circumstances, within the following 8 weeks, as not all clinics are able to offer immediate "see & treat" outpatient treatment. Polyp removal will be carried out under direct hysteroscopic vision using miniature mechanical or electrosurgical instruments, with or without the need for minor degrees of cervical dilatation and local anaesthesia (direct cervical infiltration or paracervical injection). Occasionally blind avulsion with small polypectomy forceps after hysteroscopic localisation may be required Inpatient polypectomy will be performed within 8 weeks of the initial diagnosis at outpatient hysteroscopy. Inpatient polypectomy will be performed by traditional dilatation and endometrial curettage ('D&C'), blind avulsion with or without prior localising hysteroscopy or under direct vision using an operative hysteroscope. In most instances, wide dilation of the cervical canal will be required to accommodate the larger diameter inpatient instruments within the uterus. General or spinal anaesthesia facilitates major degrees of cervical dilatation and manipulation of these larger diameter instruments within the uterine cavity
Outcomes	Primary outcome: The patient's own assessment of bleeding symptoms at 6 months, using a dichotomous outcome measure, will be used to establish if the treatment has been successful Secondary outcome: The following secondary outcomes will be assessed by a booklet sent to the women at home containing questionnaires/questions at baseline, 6, 12 and 24 months post-randomisation:

Clark 2014 (*Continued*)

	1. Shaw Menorrhagia assessment scale A multi-attribute utility, designed to measure the impact of heavy menstrual bleeding (menorrhagia) upon HRQL 2. Likert scale. All patients will be asked how their bleeding has responded to treatment using a Likert scale with four response options 3. Health-related quality of life measured by EuroQol EQ-5D Instrument 4. Visual analogue scale (VAS) It is now well established that objective measures of blood loss are not particularly relevant to women's subjective perception of bleeding symptoms
Notes	Status of the trial: completed. Query clarified by Dr Justin Clark on 08-12-2014: *"Our paper is just undergoing revision and should be published in the BMJ early next year.* *Our full NIHR HTA report will be published shortly afterwards - publication being held until the BMJ paper is in.* *I am unaware of any similar trials in female infertility - only MH Emanuel septoplasty trial and Dick Schoot RPOC morcellation study".*

Moramezi 2012

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
Notes	Recruitment status: completed. The primary study author will be contacted.

HRQL: health-related quality of life
IUI: intrauterine insemination

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

Abiri 2014

Trial name or title	The effect of hysteroscopy on successful pregnancy in IVF in the infertile women who are candidate for the first IVF cycle
Methods	Parallel-group randomised controlled trial

Abiri 2014 (*Continued*)

Participants	Inclusion criteria: age less than 38 years; BMI > 35, did not undergo hysteroscopy in the two past months, absence of uterine and tubal pathology which is incurable by hysteroscopy, couples undergoing ART with their own gametes. Exclusion criteria: embryo Donation, oocyte donation, TESE, hypothalamic amenorrhoea, OHSS, severe male factor, BMI < 35, hysteroscopy in past two months, age equal or more than 38 years, prior history of IVF, uterine and tubal pathology which is incurable by hysteroscopy
Interventions	Intervention 1: In the control group: no intervention will be done. Intervention 2: In the intervention group, hysteroscopy is performed within 14 days prior to in vitro fertilisation and If there is an abnormality in the uterine cavity, this will be correct at the same time
Outcomes	Primary outcome: biochemical pregnancy. Timepoint: 2 weeks after IVF. Method of measurement: ßHCG Secondary outcome:clinical pregnancy. Timepoint: 4 weeks after IVF. Method of measurement: vaginal sonography
Starting date	24 May 2014
Contact information	Amene Abiri Infertility department, second floor, Shariati Hospital, Jalal al Ahmad avenue, Tehran 14114, Islamic Republic of Iran Telephone: 00982184902421 e-mail: abiriir@ yahoo.com
Notes	Recruitment status: completed.

Basma 2013

Trial name or title	Hysteroscopy before first trial ICSI
Methods	Parallel-group randomised controlled trial
Participants	Primary infertility Inclusion criteria: No previous IVF/ICSI cycle Exclusion criteria: Antral follicle count (AFC) 4, Anti-mullarian hormone (AMH) ‘0.7, detectable uterine pathology by ultrasound Age minimum: 20 years Age maximum: 40 years Gender: Female
Interventions	Not reported in the registered study protocol
Outcomes	Primary outcome: clinical pregnancy with cardiac pulsation Secondary outcome: abortion, implantation rate
Starting date	01 June 2013

Basma 2013 (*Continued*)

Contact information	Elsayedamr Basma 30 Garden City Smouha, Alexandria, Egypt Telephone: 00201223106023 e-mail: elsayedamr@yahoo.com
Notes	

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

El-Khayat 2012 (*Continued*)

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
Notes	Status: recruiting.

Hare 2013

Trial name or title	Hysteroscopy before in vitro fertilization - Does it improve the outcome?
Methods	Parallel group randomised trial
Participants	Inclusion Criteria: Women submitted to IVF or ISCI treatment, age > 18 years,able to read, speak and understand Danish, written consent. Exclusion Criteria: intrauterine abnormalities, infection, BMI > 35, known intrauterine cause to the infertile condition,abuse of alcohol or drugs,untreated medical condition, pregnancy Age minimum: 18 years Age maximum: 40 years Gender: Female
Interventions	Office-hysteroscopy with biopsy
Outcomes	pregnancy rates [Time Frame: individual outcome will be evaluated within 8 weeks after IVF treatment. Over all outcome will be evaluated after 3 years.]
Starting date	January 2013
Contact information	Kristine Juul Hare, MD, PhD Hvidovre University Hospital, Danmark e-mail: kjhare@dadlnet.dk
Notes	Recruiting.

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
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	

Weiss 2005

Trial name or title	Endometrial hysteroscopy and curettage prior to embryo transfer
Methods	Parallel group randomised study
Participants	Inclusion Criteria: informed consent, in-vitro fertilisation candidate, normal blood coagulation. Exclusion Criteria: anaemia (haemoglobin < 10 mg/dL), abnormal maternal karyotype, thrombocytopenia < 140,000, any contraindication to hysteroscopy or in-vitro fertilisation Age minimum: 18 years Age maximum: 35 years Gender: Female
Interventions	Hysteroscopy and curettage
Outcomes	Primary outcomes: Endometrial receptivity, implantation rate and pregnancy rate
Starting date	December 2005
Contact information	Amir Weiss HaEmek Medicak Center and Technion, Israel Institute of Technology Telephone: 972-4-6494031 e-mail: weiss_am@clalit.org.il
Notes	Status: recruiting. The first author will be contacted.

ART: assisted reproductive technology
ßHCG: beta human chorionic gonadotropin
BMI: body mass index
ICSI: intracytoplasmic sperm injection
IUI: intrauterine insemination
IVF: in vitro fertilisation
OHSS: Ovarian hyperstimulation syndrome
TESE: Testicular sperm extraction

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	30	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.12, 2.85]
2.1 Removal of submucous fibroids only vs regular fertility-oriented intercourse	1	19	Odds Ratio (M-H, Fixed, 95% CI)	0.63 [0.09, 4.40]
2.2 Removal of mixed submucous-intramural fibroids vs regular fertility-oriented intercourse	1	11	Odds Ratio (M-H, Fixed, 95% CI)	0.5 [0.03, 7.99]

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]

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] High risk of selective outcome 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	Selective outcome reporting[2]

[1] Clinical pregnancy was defined by the presence of at least one gestational sac on ultrasound.
[2] There was high risk for selective outcome reporting bias.

WHAT'S NEW

Last assessed as up-to-date: 8 September 2014.

Date	Event	Description
29 October 2014	New citation required but conclusions have not changed	There was no change to our conclusions.
29 October 2014	New search has been performed	This review has been updated but no new studies were eligible for inclusion

HISTORY

Protocol first published: Issue 11, 2011

Review first published: Issue 1, 2013

Date	Event	Description
29 August 2014	Feedback has been incorporated	Feedback on clinical diversity in this review, received from Professor Hossam Shawki

CONTRIBUTIONS OF AUTHORS

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

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 still in the recruitment phase.

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

SOURCES OF SUPPORT

Internal sources

- CEBAM, Belgium.

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. We assessed all six items including blinding of participants, personnel and outcome assessors in the final review as opposed to the protocol.

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.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Female; Humans; Pregnancy