Cochrane Library

Cochrane Database of Systematic Reviews

Screening hysteroscopy in subfertile women and women undergoing assisted reproduction (Protocol)

Kamath MS, Bosteels J, D'Hooghe TM, Seshadri S, Weyers S, Mol BWJ, Broekmans FJ, Sunkara SK

Kamath MS, Bosteels J, D'Hooghe TM, Seshadri S, Weyers S, Mol BWJ, Broekmans FJ, Sunkara SK.
Screening hysteroscopy in subfertile women and women undergoing assisted reproduction.
Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD012856.
DOI: 10.1002/14651858.CD012856.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Screening hysteroscopy in subfertile women and women undergoing assisted reproduction

Mohan S Kamath[1], Jan Bosteels[2], Thomas M D'Hooghe[3], Srividya Seshadri[4], Steven Weyers[5], Ben Willem J Mol[6], Frank J Broekmans[7], Sesh Kamal Sunkara[8]

[1]Reproductive Medicine Unit, Christian Medical College and Hospital, Vellore, India. [2]Academic Centre for General Practice, Cochrane Belgium, Leuven, Belgium. [3]Leuven University Fertility Centre, University Hospital Gasthuisberg, Leuven, Belgium. [4]The Centre for Reproductive & Genetic Health, London, UK. [5]Obstetrics and Gynaecology, University Hospital Ghent, Ghent, Belgium. [6]Discipline of Obstetrics and Gynaecology, School of Medicine, Robinson Research Institute, The University of Adelaide, Adelaide, Australia. [7]Department of Reproductive Medicine and Gynecology, University Medical Center, Utrecht, Netherlands. [8]Reproductive Medicine Unit, Queen's Hospital, Romford, UK

Contact address: Mohan S Kamath, Reproductive Medicine Unit, Christian Medical College and Hospital, Ida Scudder Road, Vellore, Tamil Nadu, 632004, India. dockamz@gmail.com.

Editorial group: Cochrane Gynaecology and Fertility Group.
Publication status and date: New, published in Issue 11, 2017.

Citation: Kamath MS, Bosteels J, D'Hooghe TM, Seshadri S, Weyers S, Mol BWJ, Broekmans FJ, Sunkara SK. Screening hysteroscopy in subfertile women and women undergoing assisted reproduction. *Cochrane Database of Systematic Reviews* 2017, Issue 11. Art. No.: CD012856. DOI: 10.1002/14651858.CD012856.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effectiveness and safety of screening hysteroscopy in subfertile women undergoing evaluation for infertility and subfertile women undergoing IVF.

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 or due to an impairment of a person's capacity either as an individual or with his/her partner" according to the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of assisted reproductive technology (Zegers-Hochschild 2017). 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, and represents 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 numerous technological advances, live-birth rates following in vitro fertilisation (IVF) are between 21% and 25% (Mansour 2014; European IVF-Monitoring Consortium (EIM) 2016). Embryo implantation remains one of the crucial steps that determine the success of an IVF cycle. Uterine or embryonic factors could make a major contribution to the success of IVF (Taylor 2008; Singh 2011). Even after transferring euploid embryos following pre-implantation genetic screening, pregnancy rates are only around 64% (Fiorentino 2014). In recurrent implantation failure (RIF), implantation does not occur despite transfer of at least two to four good-quality embryos, and treatment of women with RIF remains a challenge to clinicians (Coughlan 2014; Polanski 2014).

Description of the intervention

Hysteroscopy is performed for the evaluation or treatment of the uterine cavity, tubal ostia, and endocervical canal. Indications include uterine bleeding disorders, Müllerian tract anomalies, retained intrauterine contraceptives or other foreign bodies, 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. During hysteroscopy, the instrument is passed through the cervix into the uterine cavity. For optimal visualisation, a distension medium, commonly saline, is used to expand the uterine cavity. The hysteroscope consists of a rigid telescope with a proximal eyepiece and a distal objective lens that can be angled at 0° to allow direct viewing or offset at various angles to provide a fore-oblique view. 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 of between 4.0 and 5.5 mm. The sheath system contains one or two 1.6- to 2.0-millimetre working channels for the insertion of small biopsy forceps, scissors, retraction loops and morcellators, or unipolar or bipolar electrodiathermy instruments.

Screening hysteroscopy is carried out in asymptomatic woman without any detectable uterine cavity abnormalities on pelvic imaging. Hysteroscopy is now a commonly performed gynaecological procedure with low complication rates of 0.1% to 0.95% (Jansen 2000). It can be carried out in an outpatient setting without general or regional anaesthesia. Various methods of pain relief are employed such as local, oral, or intravenous analgesia either alone or in combination (Ahmad 2010). It is considered as gold standard for the diagnosis of uterine cavity pathology (Taylor 2008; Bosteels 2015)

In clinical practice, evaluation of the uterine cavity is usually done with a transvaginal ultrasound scan (TVS) prior to IVF. Due to the perceived advantages of hysteroscopy over TVS, such as the simultaneous detection and treatment of intrauterine pathologies, use of pre-IVF hysteroscopy has gained widespread acceptance (Campo 2014). Although pre-IVF hysteroscopy was initially offered in women with RIF, it is currently being proposed even before the first IVF cycle (Dicker 1992; Golan 1992; La Sala 1998; Raju 2006; El-Nashar 2011; Yu 2012; Kilic 2013).

How the intervention might work

It is assumed that 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 as to how endometrial polyps, submucous fibroids, intrauterine adhesions, and uterine septa may impair implantation of the human embryo; nevertheless, the precise mechanisms of action through which each one of these cavity abnormalities affects this essential reproductive process are poorly understood. The foetal-maternal conflict hypothesis tries to explain how a successful pregnancy may establish itself despite the intrinsic genomic instability of human embryos through the specialist functions of the endometrium, in particular its capacity for cyclic spontaneous decidualisation, shedding, and regeneration. An excellent in-depth review linking basic research of human implantation with clinical practice can be found elsewhere (Lucas 2013).

Screening hysteroscopy in woman prior to IVF may reveal intrauterine pathology that may not be detected by routine TVS. The reported rates of intrauterine pathology in women undergoing first IVF, Smit 2016, and women with RIF, El-Toukhy 2016, were 12% and 27%, respectively. Hysteroscopy allows detection and treatment of many of these intrauterine pathologies, which may improve IVF outcomes (Oliveira 2003). Cervical dilation during pre-IVF hysteroscopy may facilitate subsequent embryo transfers, which could possibly improve outcomes. Another proposed mechanism to help improve IVF outcomes following hysteroscopy is local endometrial injury caused during the invasive procedure. The inflammatory reaction following endometrial injury leads to release of cytokines and growth factors that may help implantation and improve clinical pregnancy rates following IVF (Barash 2003; Nastri 2015).

Why it is important to do this review

Although detection of intrauterine pathologies in women with normal TVS prior to IVF is perceived as one of the benefits of performing hysteroscopy, it is not clear whether treating these

pathologies improves outcomes (Oliveira 2003; Pundir 2014; Smit 2016). In a randomised controlled trial (RCT), live-birth rates did not differ significantly when women with treated intrauterine abnormalities were compared to women with untreated intrauterine abnormalities following hysteroscopy prior to IVF (Smit 2016). An earlier systematic review found a beneficial effect from hysteroscopy in a subgroup of women undergoing IVF with two previously failed IVF attempts (El-Toukhy 2008). Another systematic review evaluating the role of hysteroscopy in women with normal TVS undergoing their first IVF cycle found significantly higher live-birth rates following hysteroscopy compared to controls, although it included mainly non-randomised trials, which could contribute to bias (Pundir 2014). Recently two large multicentre trials found no benefit of hysteroscopy in women prior to their first IVF cycle and in women with RIF (El-Toukhy 2016; Smit 2016). Current guidelines do not advocate routine use of screening hysteroscopy during the initial infertility work-up (Crosignani 2000; NICE 2013). Due to prevailing ambiguity in the literature regarding the role of screening hysteroscopy in women with normal TVS during infertility work-up and prior to IVF, it is important to conduct a systematic appraisal of the literature.

OBJECTIVES

To assess the effectiveness and safety of screening hysteroscopy in subfertile women undergoing evaluation for infertility and subfertile women undergoing IVF.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished RCTs will be eligible for inclusion. We will exclude non-randomised studies and quasi-randomised trials. We will include cross-over trials if individually randomised women are the unit of analysis; we will only include data from the first phase (pre-cross-over data) in the meta-analyses, as the cross-over trial is not a valid study design in the context of subfertility.

Types of participants

1. Subfertile women in whom routine imaging did not show uterine cavity abnormalities.
2. Women undergoing screening hysteroscopy prior to IVF.

We will exclude subfertile women suspected of uterine cavity abnormalities (present on any imaging techniques).

Types of interventions

We will include the following randomised comparisons.

1. A routine, screening hysteroscopy, including hysteroscopic treatment of any detected uterine cavity abnormalities versus no hysteroscopy in subfertile women undergoing evaluation for subfertility.
2. A routine, screening hysteroscopy, including hysteroscopic treatment of any detected uterine cavity abnormalities versus no hysteroscopy before IVF.

Types of outcome measures

Primary outcomes

1. Live birth or (in studies that do not report live birth) ongoing pregnancy. The live-birth delivery rate (whether or not after assisted reproduction) is defined as delivery of a live foetus after 20 completed weeks of gestational age. We will count the delivery of singleton, twin or multiple pregnancies as one live birth. The ongoing-pregnancy rate (whether or not after assisted reproduction) is defined as evidence of a gestational sac with foetal heart motion at 12 weeks, confirmed by ultrasound. We will count multiple gestational sacs as one ongoing pregnancy.
2. Adverse events: the incidence of complications due to the hysteroscopy procedure, analysed as composite measure of any adverse events (including perforation, infection, vasovagal attacks).

Secondary outcomes

1. Clinical pregnancy rate (whether or not after assisted reproduction), defined as ultrasound evidence of a gestational sac.
2. Miscarriage rate (whether or not after assisted reproduction), defined as the spontaneous loss of a clinical pregnancy that occurs before 20 completed weeks of gestation (18 weeks post fertilisation) or, if gestational age is unknown, the loss of an embryo or foetus of less than 400 g.

We will avoid excluding studies on the basis of their reported outcome measures. We will review eligible studies that could have measured the outcomes of interest. We will report any lack of data for key outcomes in the final review.

Search methods for identification of studies

We will search for all published and unpublished RCTs of routine hysteroscopy in infertile women, without language restriction and in consultation with the Cochrane Gynaecology and Fertility Group Information Specialist.

Electronic searches

We will search the following electronic databases, trial registers, and websites from inception to present:

- Cochrane Gynaecology and Fertility Group (GFG) Specialised Register, ProCite platform (Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL CRSO), web platform (Appendix 2);
- MEDLINE, Ovid platform (Appendix 3);
- Embase, Ovid platform (Appendix 4);
- PsycINFO, Ovid platform (Appendix 5);
- CINAHL (Cumulative Index to Nursing and Allied Health Literature), Ebsco platform (Appendix 6).

We will combine the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials, which appears in Section 6.4.11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebre 2011).
The Embase, PsycINFO, and CINAHL searches are combined with trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/search-filters.html).
Other electronic sources of trials will include:

- trial registers for ongoing and registered trials:
    - US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
    - World Health Organization International Trials Registry Platform (www.who.int/trialsearch/Default.aspx).
- DARE (Database of Abstracts of Reviews of Effects) on the Cochrane Library (onlinelibrary.wiley.com/o/cochrane/cochrane_cldare_articles_fs.html) for reference lists from relevant non-Cochrane reviews;
- Web of Knowledge (wokinfo.com/) (another source of trials and conference abstracts);
- OpenGrey (www.opengrey.eu/) for unpublished literature from Europe;
- LILACS (Latin American and Caribbean Health Science Information database) (regional.bvsalud.org/php/index.php?lang=en) for trials from the Portuguese- and Spanish-speaking world;
- PubMed and Google for recent trials not yet indexed in MEDLINE.

Searching other resources

Three review authors (SS, JB, and MSK) will handsearch reference lists of articles retrieved by the search and contact experts in the field to obtain additional data. We will also handsearch relevant journals and conference abstracts that are not covered in the GFG register, in liaison with the Information Specialist.

Data collection and analysis

Selection of studies

One review author (MSK) will conduct an initial screen of titles and abstracts identified by the search, after which we will retrieve the full texts of all potentially eligible studies. Three review authors (SS, JB, and MSK) will independently examine these full-text articles for compliance with the inclusion criteria and select studies eligible for inclusion in the review. We will correspond with study investigators as required to clarify study eligibility. Disagreements as to study eligibility will be resolved by discussion or by a third review author (SKS). We will document the selection process with a PRISMA flow chart.

Data extraction and management

Two review authors (one a methodologist (MSK) and one a topic area specialist (JB)) will independently extract data from eligible studies using a data extraction form designed and pilot-tested by the review authors. Any disagreements will be resolved by discussion or by a third review author (SKS). We will extract data including study characteristics and outcome data (Appendix 7). Where studies have multiple publications, the review authors will collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review, and such studies will have a single study ID with multiple references.
We will correspond with study investigators for further data on methods or results, or both, as required. We will include studies irrespective of whether outcomes are reported in a 'usable' way. In multi-arm studies, data from arms that do not meet the eligibility criteria will be excluded.

Assessment of risk of bias in included studies

Three review authors (MSK, JB, and SS) will independently assess the included studies for risk of bias using the Cochrane 'Risk of bias' assessment tool (Higgins 2011). We will assess the following items: selection (random sequence generation and allocation concealment); performance (blinding of participants and personnel); detection (blinding of outcome assessors); attrition (incomplete outcome data); reporting (selective reporting); and other bias. Disagreements will be resolved by discussion or by a fourth review author. We will describe all judgements fully and present the conclusions in the 'Risk of bias' table, which will be incorporated into the interpretation of review findings by means of sensitivity analyses (see Sensitivity analysis). Selective reporting is a type of reporting bias that affects the internal validity of an individual study. It refers to the selective reporting of some outcomes (e.g. positive outcomes) and the failure to report others (e.g. adverse events). We will take care to search for within-trial selective reporting, such as trials failing to report obvious outcomes, or reporting them in insufficient detail to allow inclusion. We will seek published protocols and compare the outcomes between the protocol and the final published study. Where identified studies fail to report the

primary outcome of live birth, but do report interim outcomes such as pregnancy, we will undertake informal assessment as to whether the interim values (e.g. pregnancy rates) are similar to those reported in studies that also report live birth.

Measures of treatment effect

For dichotomous data (e.g. live-birth rates), we will use the numbers of events in the control and intervention groups of each study to calculate risk ratios (RR). We will use Peto odds ratio (OR) for outcomes with low event rates. We will reverse the direction of effect of individual studies, if required, to ensure consistency across trials. We will present 95% confidence intervals (CI) for all outcomes. Where data to calculate RRs or ORs are not available, we will utilise the most detailed numerical data available that may facilitate similar analyses of included studies (e.g. test statistics, P values). We will compare the magnitude and direction of effect reported by studies with how they are presented in the review, taking account of legitimate differences.

Unit of analysis issues

The primary analysis will be per woman randomised; we will include per-pregnancy data for some outcomes (for the outcome miscarriage). If studies report only 'per-cycle' data, we will contact the study authors to request 'per-woman' data. Data that do not allow valid analysis (e.g. per-cycle data) will be briefly summarised in an Additional table and will not be meta-analysed. We will count multiple live births (e.g. twins or triplets) as one live-birth event. We will include only first-phase data from cross-over trials.

Dealing with missing data

We will analyse the data on an intention-to-treat basis to the greatest degree possible and will attempt to obtain missing data from the original authors. Where these data are unobtainable, we will undertake imputation of individual values for live birth only. We will assume live births not to have occurred in women without a reported outcome. For other outcomes, we will analyse only the available data.

Any imputation undertaken will be subjected to sensitivity analysis (see Sensitivity analysis). If studies report sufficient detail to calculate mean differences but no information on associated standard deviation, we will assume the outcome to have standard deviation equal to the highest standard deviation from other studies within the same analysis.

Assessment of heterogeneity

We will consider whether the clinical and methodological characteristics of the included studies are sufficiently similar for meta-analysis to provide a clinically meaningful summary. We will assess statistical heterogeneity using the I^2 statistic. An I^2 measurement greater than 50% will be taken to indicate substantial heterogeneity (Higgins 2011).

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, the review authors will aim to minimise the potential impact of these biases by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If there are 10 or more studies in an analysis, we will use a funnel plot to explore the possibility of small-study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies).

Data synthesis

One review author (SS) will enter the data and perform the statistical analysis using Review Manager 5 (RevMan 2014). If the studies are sufficiently similar, we will combine the data using a fixed-effect model for the following comparisons.

- Hysteroscopy versus no hysteroscopy for subfertile women.
- Hysteroscopy versus no hysteroscopy for women undergoing IVF.

We will display an increase in the odds of a particular outcome, which may be beneficial (e.g. live birth) or detrimental (e.g. adverse effects of the hysteroscopy) graphically in the meta-analyses to the right of the centre-line and a decrease in the odds of an outcome to the left of the centre-line.

Subgroup analysis and investigation of heterogeneity

Where data are available, we will conduct subgroup analyses to determine the separate evidence within the following subgroups.

- According to the presence or absence of uterine cavity abnormalities at hysteroscopy.

We will conduct the following subgroup analyses within the IVF population.

- Women undergoing first IVF.
- Women with two or more failed IVF cycles.

The interpretation of the statistical analysis for subgroups is difficult. We will mainly use the subgroup analysis to substantiate certain hypotheses concerning the results. In case no RCTs are retrieved for some subgroup analysis, the absence of literature will be reported and identified knowledge gaps will be described.

Sensitivity analysis

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

- eligibility had been restricted to studies without high risk of bias (not at high risk of bias in any domain and at low risk for randomisation procedures);
- a random-effects model had been adopted;
- alternative imputation strategies had been implemented;
- the summary effect measure had been risk ratio rather than odds ratios;
- the primary outcome had been limited to live birth.

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

We will prepare a 'Summary of findings' table using GRADEpro GDT (GRADEpro GDT 2014) and Cochrane methods (Higgins 2011). This table will evaluate the overall quality of the body of evidence for all review outcomes. We will assess the quality of the evidence using GRADE criteria (risk of bias, consistency of effect, imprecision, indirectness, and publication bias). Two review authors will independently make judgements about evidence quality (high, moderate, low, or very low), with any disagreements resolved by discussion. Judgements will be justified, documented, and incorporated into reporting of results for each outcome.
We plan to extract study data, format our comparisons in data tables, and prepare a 'Summary of findings' table before writing the results and conclusions of our review.

ACKNOWLEDGEMENTS

Cochrane Gynaecology and Fertility Group (CGF). We wish to thank Helen Nagels, CGF Managing Editor, and Marian Showell, CGF Information Specialist.

Biomedical Library Gasthuisberg, Catholic University, Leuven, Belgium. Many thanks to Jens De Groot for skilful assistance in developing the literature search strategy.

REFERENCES

Additional references

Ahmad 2010
Ahmad G, O'Flynn H, Attarbashi S, Duffy JM, Watson A. Pain relief for outpatient hysteroscopy. *Cochrane Database of Systematic Reviews* 2010, Issue 11. [DOI: 10.1002/14651858.CD007710.pub2

Barash 2003
Barash A, Dekel N, Fieldust S, Segal I, Schechtman E, Granot I. Local injury to the endometrium doubles the incidence of successful pregnancies in patients undergoing in vitro fertilization. *Fertility and Sterility* 2003;**79**(6):1317–22.

Boivin 2007
Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Human Reproduction* 2007;**22**(6):1506–12.

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

Campo 2014
Campo R, Meier R, Dhont N, Mestdagh G, Ombelet W. Implementation of hysteroscopy in an infertility clinic: the one-stop uterine diagnosis and treatment. *Facts, Views & Vision in ObGyn* 2014;**6**(4):234–9.

Coughlan 2014
Coughlan C, Ledger W, Wang Q, Liu F, Demirol A, Gurgan T, et al. Recurrent implantation failure: definition and management. *Reproductive Biomedicine Online* 2014;**28**(1):14–38.

Crosignani 2000
Crosignani PG, Rubin BL. Optimal use of infertility diagnostic tests and treatments. The ESHRE Capri Workshop Group. *Human Reproduction* 2000;**15**(3):723–32.

Dicker 1992
Dicker D, Ashkenazi J, Feldberg D, Farhi J, Shalev J, Ben Rafael Z. The value of repeat hysteroscopic evaluation in patients with failed in vitro fertilisation cycles. *Fertility and Sterility* 1992;**58**:833–5.

El-Nashar 2011
El-Nashar IH, Nasr A. The role of hysteroscopy before intracytoplasmic sperm injection (ICSI): a randomized controlled trial. *Fertility and Sterility* 2011;**96**:0015-0282; suppl S266.

El-Toukhy 2008
El-Toukhy T, Sunkara SK, Coomarasamy A, Grace J, Khalaf Y. Outpatient hysteroscopy and subsequent IVF cycle outcome: a systematic review and meta-analysis. *Reproductive Biomedicine Online* 2008;**16**(5):712–9.

El-Toukhy 2016
El-Toukhy T, Campo R, Khalaf Y, Tabanelli C, Gianaroli L, Gordts SS, et al. Hysteroscopy in recurrent in-vitro

fertilisation failure (TROPHY): a multicentre, randomised controlled trial. *Lancet* 2016;**387**:2614–21.

European IVF-Monitoring Consortium (EIM) 2016
European IVF-Monitoring Consortium (EIM), European Society of Human Reproduction and Embryology (ESHRE), Kupka MS, D'Hooghe T, Ferraretti AP, de Mouzon J, Erb K, Castilla JA, et al. Assisted reproductive technology in Europe, 2011: results generated from European registers by ESHRE. *Human Reproduction* 2016; **31**(2):233–48.

Fiorentino 2014
Fiorentino F, Bono S, Biricik A, Nuccitelli A, Cotroneo E, Cottone G, et al. Application of next-generation sequencing technology for comprehensive aneuploidy screening of blastocysts in clinical preimplantation genetic screening cycles. *Human Reproduction* 2014;**29**(12):2802–13.

Golan 1992
Golan A, Ron El R, Herman A, Soffer Y, Bukovsky I, Caspi E. Diagnostic hysteroscopy: its value in an in-vitro fertilisation/embryo transfer unit. *Human Reproduction* 1992;**7**:1433–4.

GRADEpro GDT 2014 [Computer program]
GRADE Working Group, McMaster University. GRADEpro GDT. Version accessed XXX. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011 Available from www.cochrane–handbook.org.

Jansen 2000
Jansen FW, Vredevoogd CB, van Ulzen K, Hermans J, Trimbos JB, Trimbos-Kemper TC. Complications of hysteroscopy: a prospective, multicenter study. *Obstetrics & Gynecology* 2000;**96**(2):266–70.

Kilic 2013
Kilic Y, Bastu E, Ergun B. Validity and efficacy of office hysteroscopy before in vitro fertilization treatment. *Archives of Gynecology and Obstetrics* 2013;**287**:577–81.

La Sala 1998
La Sala GB, Montanari R, Dessanti L, Cigarini C. The role of diagnostic hysteroscopy and endometrial biopsy in assisted reproductive technologies. *Fertility and Sterility* 1998;**70**:378–80.

Lefebre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Lucas 2013
Lucas ES, Salker MS, Brosens JJ. Uterine plasticity and reproductive fitness. *Reproductive Biomedicine Online* 2013; **27**:664–72.

Mansour 2014
Mansour R, Ishihara O, Adamson GD, Dyer S, de Mouzon J, Nygren KG, et al. International Committee for Monitoring Assisted Reproductive Technologies World Report: Assisted Reproductive Technology 2006. *Human Reproduction* 2014;**29**:1536–51.

Nastri 2015
Nastri CO, Lensen SF, Gibreel A, Raine-Fenning N, Ferriani RA, Bhattacharya S, et al. Endometrial injury in women undergoing assisted reproductive techniques. *Cochrane Database of Systematic Reviews* 2015, Issue 3. [DOI: 10.1002/14651858.CD009517.pub3

NICE 2013
National Institute for Health and Care Excellence. Fertility: assessment and treatment for people with fertility problems. NICE guideline (CG156) 2013.

Oliveira 2003
Oliveira FG, Abdelmassih VG, Diamond MP, Dozortsev D, Nagy ZP, Abdelmassih R. Uterine cavity findings and hysteroscopic interventions in patients undergoing in vitro fertilization-embryo transfer who repeatedly cannot conceive. *Fertility and Sterility* 2003;**80**(6):1371–5.

Polanski 2014
Polanski LT, Baumgarten MN, Quenby S, Brosens J, Campbell BK, Raine-Fenning NJ. What exactly do we mean by 'recurrent implantation failure'? A systematic review and opinion. *Reproductive Biomedicine Online* 2014; **28**(4):409–23.

Pundir 2014
Pundir J, Pundir V, Omanwa K, Khalaf Y, El-Toukhy T. Hysteroscopy prior to the first IVF cycle: a systematic review and meta-analysis. *Reproductive Biomedicine Online* 2014;**28**(2):151–61.

Raju 2006
Raju RG, Kumari SG, Krishna KM, Prakash GJ, Madan K. Assessment of uterine cavity by hysteroscopy in assisted reproduction programme and its influence on pregnancy outcome. *Archives of Gynecology and Obstetrics* 2006;**274**: 160–4.

Ray 2012
Ray A, Shah A, Gudi A, Homburg R. Unexplained infertility: an update and review of practice. *Reproductive BioMedicine Online* 2012;**24**:591–602.

RevMan 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Singh 2011
Singh M, Chaudhry P, Asselin E. Bridging endometrial receptivity and implantation: network of hormones, cytokines, and growth factors. *J Endocrinol* 2011;**210**(1): 5–14.

Smit 2016
Smit JG, Kasius JC, Eijkemans MJ, Koks CA, van Golde R, Nap AW, et al. Hysteroscopy before in-vitro fertilisation (inSIGHT): a multicentre, randomised controlled trial. *Lancet* 2016;**387**(10038):2622–9.

Taylor 2008
Taylor E, Gomel V. The uterus and fertility. *Fertility and Sterility* 2008;**89**:1–16.

Yu 2012
Yu HT, Wang CJ, Lee CL. The role of diagnostic hysteroscopy before the first in vitro fertilization/ intracytoplasmic sperm injection cycle. *Archives of Gynecology and Obstetrics* 2012;**286**:1323–8.

Zegers-Hochschild 2017
Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, et al. The International Glossary on Infertility and Fertility Care, 2017. *Fertility and Sterility* 2017;**108**(3):393–406.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Cochrane Gynaecology and Fertility Group Specialised Register search strategy

From inception to present
Procite platform
Keywords CONTAINS "hysteroscopic "or "hysteroscope diameter" or "hysteroscope size" or "hysteroscopy" or "hysteroscopy, techniques" or "hysteroscopy-second look" or "hysterscope" or "uterine cavity assessment" or "mini-hysteroscopy" or "minihysteroscopy" or "endometrial polypectomy" or "endometrial polyps" or "endoscopy" or Title CONTAINS "hysteroscopic "or "hysteroscope diameter"or "hysteroscope size" or "hysteroscopy" or "hysteroscopy, techniques" or "hysteroscopy-second look" or "hysterscope" or "uterine cavity assessment" or "mini-hysteroscopy" or "minihysteroscopy" or "endometrial polypectomy" or "endometrial polyps" or "endoscopy"
AND
Keywords CONTAINS "IVF" or "ICSI" or "subfertility" or "in vitro fertilisation" or "in vitro fertilization" or "intracytoplasmic sperm injection" or "assisted conception" or "assisted reproduction" or "ART" or "infertility" or "IUI" or "Intrauterine Insemination" or "artificial insemination" or "ovarian hyperstimulation" or "ovarian stimulation" or "ovulation induction" or "COH" or "controlled ovarian " or "insemination" or "insemination-intrauterine" or "subfertility-female" or "IUI" or "recurrent miscarriage" or "pregnancy" or Title CONTAINS "IVF" or "ICSI" or "subfertility" or "in vitro fertilisation" or "in vitro fertilization" or "intracytoplasmic sperm injection" or "assisted conception" or "assisted reproduction" or "ART" or "infertility" or "IUI" or "Intrauterine Insemination" or "artificial insemination" or "ovarian hyperstimulation" or "ovarian stimulation" or "ovulation induction" or "COH" or "controlled ovarian " or "insemination" or "insemination-intrauterine" or "subfertility-female" or "IUI" or "pregnancy"

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

From inception to present
Cochrane Register of Studies Online (CRSO) web platform
#1 MESH DESCRIPTOR Hysteroscopy EXPLODE ALL TREES
#2 Hysteroscop*:TI,AB,KY
#3 Uteroscop*:TI,AB,KY
#4 minihysteroscop*:TI,AB,KY
#5 (Uter* adj3 Endoscop*):TI,AB,KY
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 MESH DESCRIPTOR Infertility, Female EXPLODE ALL TREES
#8 MESH DESCRIPTOR Reproductive Techniques, Assisted EXPLODE ALL TREES
#9 (subfertil* or infertil*):TI,AB,KY
#10 (IVF or ICSI):TI,AB,KY
#11 (artificial insemination):TI,AB,KY
#12 (assisted reproducti*):TI,AB,KY

#13 (intrauterine insemination):TI,AB,KY
#14 IUI:TI,AB,KY
#15 pregnancy:TI,AB,KY
#16 conception:TI,AB,KY
#17 fertility:TI,AB,KY
#18 MESH DESCRIPTOR Abortion, Habitual EXPLODE ALL TREES
#19 miscarriage*:TI,AB,KY
#20 (pregnancy loss):TI,AB,KY
#21 conceive:TI,AB,KY
#22 MESH DESCRIPTOR Gynatresia EXPLODE ALL TREES
#23 Gynatresia:TI,AB,KY
#24 (implant* adj3 failure*):TI,AB,KY
#25 IVF-ET:TI,AB,KY
#26 (ovulation induction):TI,AB,KY
#27 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26
#28 #6 AND #27

Appendix 3. MEDLINE search strategy

From 1946 to present
Ovid platform
1 exp Hysteroscopy/
2 Hysteroscop$.tw.
3 Uteroscop$.tw.
4 minihysteroscop$.tw.
5 (Uter$ adj3 Endoscop$).tw.
6 or/1-5
7 exp Infertility/
8 subfertil$.tw.
9 (IVF or ICSI).tw.
10 artificial insemination.tw.
11 assisted conception.tw.
12 intrauterine insemination.tw.
13 iui.tw.
14 reproductive techniques, assisted/ or exp embryo transfer/ or exp fertilization in vitro/ or exp sperm injections, intracytoplasmic/ or in vitro oocyte maturation techniques/ or exp insemination, artificial/ or exp ovulation induction/ or exp superovulation/ (50541)
15 exp Infertility, Female/
16 Infertil$.tw.
17 pregnancy.tw.
18 conception.tw.
19 fertility.tw.
20 Abortion, Habitual/
21 miscarriage$.tw.
22 recurrent pregnancy loss$.tw.
23 conceive.tw.
24 Gynatresia/
25 (implant$ adj3 failure$).tw.
26 IVF-ET.tw.
27 ovulation induction.tw.
28 or/7-27
29 randomized controlled trial.pt.

30 controlled clinical trial.pt.
31 randomized.ab.
32 randomised.ab.
33 placebo.tw.
34 clinical trials as topic.sh.
35 randomly.ab.
36 trial.ti.
37 (crossover or cross-over or cross over).tw.
38 or/29-37
39 exp animals/ not humans.sh.
40 38 not 39
41 6 and 28 and 40

Appendix 4. Embase search strategy

From 1980 to present
Ovid platform
1 exp Hysteroscopy/
2 Hysteroscop$.tw.
3 Uteroscop$.tw.
4 minihysteroscop$.tw.
5 (Uter$ adj3 Endoscop$).tw.
6 or/1-5
7 subfertil$.tw.
8 (IVF or ICSI).tw.
9 artificial insemination.tw.
10 assisted conception.tw.
11 intrauterine insemination.tw.
12 iui.tw.
13 Infertil$.tw.
14 pregnancy.tw.
15 conception.tw.
16 fertility.tw.
17 miscarriage$.tw.
18 recurrent pregnancy loss$.tw.
19 conceive.tw.
20 (implant$ adj3 failure$).tw.
21 IVF-ET.tw.
22 ovulation induction.tw.
23 exp infertility/ or exp female infertility/ or exp infertility therapy/
24 assisted reproducti$.tw.
25 exp intracytoplasmic sperm injection/
26 exp artificial insemination/
27 exp ovulation induction/
28 exp superovulation/
29 exp recurrent abortion/
30 or/7-29
31 6 and 30
32 Clinical Trial/
33 Randomized Controlled Trial/
34 exp randomization/
35 Single Blind Procedure/

36 Double Blind Procedure/
37 Crossover Procedure/
38 Placebo/
39 Randomi?ed controlled trial$.tw.
40 Rct.tw.
41 random allocation.tw.
42 randomly allocated.tw.
43 allocated randomly.tw.
44 (allocated adj2 random).tw.
45 Single blind$.tw.
46 Double blind$.tw.
47 ((treble or triple) adj blind$).tw.
48 placebo$.tw.
49 prospective study/
50 or/32-49
51 case study/
52 case report.tw.
53 abstract report/ or letter/
54 or/51-53
55 50 not 54
56 31 and 55

Appendix 5. PsycINFO search strategy

From 1806 to present
Ovid platform
1 subfertil$.tw.
2 (IVF or ICSI).tw.
3 artificial insemination.tw.
4 assisted conception.tw.
5 intrauterine insemination.tw.
6 iui.tw.
7 Infertil$.tw.
8 pregnancy.tw.
9 conception.tw.
10 fertility.tw.
11 miscarriage$.tw.
12 recurrent pregnancy loss$.tw.
13 conceive.tw.
14 (implant$ adj3 failure$).tw.
15 IVF-ET.tw.
16 ovulation induction.tw.
17 assisted reproducti$.tw.
18 exp Infertility/
19 exp Reproductive Technology/
20 exp Spontaneous Abortion/
21 or/1-20
22 Hysteroscop$.tw.
23 21 and 22

Appendix 6. CINAHL search strategy

From 1961 to present
Ebsco platform

#	Query
S47	S32 AND S46
S46	S33 OR S34 or S35 or S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45
S45	TX allocat* random*
S44	(MH "Quantitative Studies")
S43	(MH "Placebos")
S42	TX placebo*
S41	TX random* allocat*
S40	(MH "Random Assignment")
S39	TX randomi* control* trial*
S38	TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S37	TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S36	TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S35	TX clinic* n1 trial*
S34	PT Clinical trial
S33	(MH "Clinical Trials+")
S32	S6 AND S31
S31	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30
S30	TX ovulation induction
S29	TX IVF-ET
S28	TX (implant* N3 fail*)
S27	TX conceive

(*Continued*)

S26	TX (recurrent pregnancy loss)
S25	TX miscarriage
S24	(MM "Abortion, Habitual")
S23	TX fertility
S22	TX conception
S21	TX pregnancy
S20	TX Infertil*
S19	TX superovulation
S18	(MM "Ovulation Induction")
S17	TX (sperm injection* intracytoplasmic)
S16	(MM "Fertilization in Vitro")
S15	(MH "Reproduction Techniques+")
S14	TX iui
S13	TX intrauterine insemination
S12	TX assisted conception
S11	(MM "Insemination, Artificial")
S10	TX artificial insemination
S9	TX (IVF or ICSI)
S8	TX subfertil*
S7	(MM "Infertility") OR (MM "Embryo Transfer")
S6	S1 OR S2 OR S3 OR S4 OR S5
S5	TX (Uter* N3 Endoscop*)
S4	TX minihysteroscop*
S3	TX Uteroscop*

(*Continued*)

S2	TX Hysteroscop*
S1	(MM "Hysteroscopy")

Appendix 7. Data extraction form

Study information			
1. Ref ID			
2. First author			
3. Year			
4. Published	q Yes	q No	
5. Language			

Criteria for eligibility:		**YES**	**NO**
Patients:	Couples undergoing hysteroscopy prior to IVF/ICSI	q	q
Intervention	Screening/routine hysteroscopy a) Prior to the first IVF/ICSI cycle b) Prior to 2 or more failed IVF cycles	q	q
Comparison	No hysteroscopy	q	q
Outcome	**Primary:** Live-birth rate (per randomised couple) **Secondary:** Clinical pregnancy rate (per randomised couple) *(positive pregnancy test, gestational sac on ultrasound)* Multiple pregnancy rate (per randomised couple) Miscarriage rate (per randomised couple) Congenital anomalies (per randomised couple) **Additional:**	q q q q q q q q q	q q q q q q q q q

Study characteristics	
Design	
1. Study design	q RCT q Parallel *(intervention vs control)*

(*Continued*)

	q Cross-over *(participants used as intervention and control group)* q ……. **Quotes:** ……	
2. Setting	q Single-centre	q Multicentre
	Country: ……	
Participants: in- and exclusion		
3. Study criteria for patient inclusion	_____ _____	
4. Study criteria for patient exclusion	_____ _____	
5. Description control/ comparison treatment	……	
Baseline characteristics		
Previous IVF and/or ICSI treatment	q Reported	q Not reported
Intervention		
Embryo transfer after IVF, ICSI		
1. Time of randomisation during cycle	q Prior to commencement of treatment cycle	
2. Nature of intervention	q Hysteroscopy q No hysteroscopy	
3. Timing of intervention	q Late luteal phase in the preceding cycle Follicular phase in the preceding cycle	

CONTRIBUTIONS OF AUTHORS

MSK and JB drafted the protocol; SS contributed with comments and references; and SKS corrected the draft and helped with references.

TDH, SW, BWM and FB gave clinical and methodological advice, reviewed and commented on the protocol.

DECLARATIONS OF INTEREST

Mohan S Kamath, Jan Bosteels, Srividya Seshadri, Steven Weyers, and Sesh Kamal Sunkara have no conflicts of interest to declare.

Thomas M D'Hooghe, MD, PhD, is a Professor in Reproductive Medicine, Department of Development and Regeneration, University of Leuven (KU Leuven), Belgium, and Professor Adjunct, Department of Obstetrics and Gynecology, Yale University, New Haven, USA. Since October 2015, he has been appointed as Vice-President and Head of Global Medical Affairs Fertility, Merck KGaA, Darmstadt, Germany. His participation in this publication is part of his academic work. Merck KGaA is not involved in the development or marketing of products related to hysteroscopy. Professor D'Hooghe's employment by Merck is not in breach of Cochrane's Commercial Sponsorship Policy (clause 2) as he does not have a real or potential financial interest in the outcome of this review. This matter was referred to Cochrane's Funding Arbiter for advice.

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

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

SOURCES OF SUPPORT

Internal sources

- Cochrane South Asia, Prof. BV Moses Centre for Evidence-Informed Health Care and Health Policy, Christian Medical College, Vellore, India.

External sources

- None, Other.