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Efficacy of hysteroscopy in improving reproductive outcomes of infertile couples: a systematic review and meta-analysis

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BACKGROUND: The scientific community has been re-evaluating the clinical relevance of hysteroscopy in the diagnosis and treatment of uterine factors and its role in the infertility work-up, thanks to its potential capability to improve reproductive outcomes and reduce time to pregnancy.

OBJECTIVE AND RATIONALE: The objective of this systematic review and meta-analysis was to assess the efficacy of diagnostic and operative hysteroscopy in improving the live birth rate (LBR) of infertile women, with and without intrauterine abnormalities, at any stage of the infertility work-up.

SEARCH METHODS: PubMed, Embase, the Cochrane Library and the Clinical Trials Registry using Medical Subject Headings and free text terms were searched up to June 2014, without language or year restrictions. Randomized controlled trials (RCTs) enrolling infertile women with no suspected intrauterine cavity abnormalities and comparing hysteroscopy versus no hysteroscopy at any stage of the diagnostic work-up, but prior to the first attempt of standard IVF or ICSI or after (one or more) failed attempts of IVF/ICSI were included. RCTs enrolling infertile women with intrauterine abnormalities and comparing operative versus diagnostic hysteroscopy were also included. Risk of bias was assessed using the criteria recommended by the Cochrane Collaboration and the overall quality of evidence was assessed using the GRADE approach. Results were pooled by meta-analysis using the random effect model.

OUTCOMES: The primary outcome evaluated was the LBR, while secondary outcomes were pregnancy rate, miscarriage rate and procedure-related complications. Five hundred and eighty-eight records were retrieved after removing duplicates. Nine studies were included, with 2976 participants. Four studies included infertile women with one or more failed IVF/ICSI cycles. Two studies included infertile women who were candidates for their first IVF/ICSI. One study included candidates both for first IVF/ICSI and with one or more failed IVF/ICSI cycles. Two studies included infertile women affected by uterine fibroids and endometrial polyps, who had not received IVF/ICSI nor were candidates. Seven studies were included in the meta-analysis. Comparing hysteroscopy with no hysteroscopy prior to any (first or subsequent) IVF/ICSI attempt in infertile women without intrauterine abnormalities, there was very low-quality evidence that hysteroscopy increased LBR (relative risk (RR) 1.48, 95% confidence interval (CI) 1.20–1.81; three studies with 1088 participants) and moderate quality evidence that it increased pregnancy rate (RR 1.45, 95% CI 1.26–1.67; seven studies, 2545 participants). Results on pregnancy rate were confirmed in the subgroup analysis of five studies including only women with one or more implantation failures (RR 1.41, 95% CI 1.14–1.75) and three studies where hysteroscopy was performed before the first IVF/ICSI attempt (RR 1.55, 95% CI 1.26–1.91). Comparing operative hysteroscopy for intrauterine abnormalities in infertile women with already diagnosed polyps or fibroids, there was low-quality evidence that operative hysteroscopy increases pregnancy rate (RR 2.13, 95% CI 1.56–2.92). None of the studies comparing operative versus diagnostic hysteroscopy assessed LBR.

WIDER IMPLICATIONS: Robust and high-quality RCTs are still needed before hysteroscopy can be regarded as a first-line procedure in all infertile women, especially during the basal clinical assessment of the couple, when assisted reproductive treatment is not indicated yet.

Key words: hysteroscopy / infertility / live birth rate / meta-analysis / pregnancy rate / polyps / myomas / systematic review

Introduction

Background

Infertility is a critical component of reproductive health with high social relevance. It has been estimated that 72.4 million couples are infertile worldwide and that 40.5 million of these are currently seeking fertility treatment (Boivin *et al.*, 2007).

Currently, the definition of infertility is a subject on which agreement is still lacking in the literature. The guidelines from the National Institute for Health and Clinical Excellence report (NICE, 2013) that infertility is a failure to conceive after a period of 2 years, whereas Gnoth *et al.* (2003) argue that the question of subfertility should be raised after six cycles of unprotected intercourse without conception, irrespective of age.

The most commonly accepted definition of infertility is that of the International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) revised glossary of assisted reproductive technology (ART) (Zegers-Hochschild *et al.*, 2009), which describes infertility as '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'.

Contributors to infertility include ovulatory (30%), male (25%), tubal (25%), coital (5%) and cervical (<5%) problems. All these factors can act individually or in various combinations (Impey and Child, 2008). When no specific contributors to infertility are detected after the completion of standard fertility investigations, the expression 'unexplained' infertility is used (Smith *et al.*, 2003). The potential causes of unexplained infertility have been described as disturbances in endocrinological balance, immunology, genetics and reproductive physiology (Pellicer *et al.*, 1998).

The initial assessment of the infertile couple relies on specific investigations including tests of ovulation and tubal patency, as well as semen analysis. Another investigation of infertile women is evaluation of the uterine factor, given that the uterine cavity and its inner layer, the endometrium are considered to be fundamental for the implantation of the embryo and normal placentation (Valli *et al.*, 1995; Fabres *et al.*, 1998; Polisseni *et al.*, 2003; Cicinelli *et al.*, 2005; Taylor *et al.*, 2008; Revel, 2012; SEGI guidelines, 2014).

Currently, the gold standard technique for uterine factor evaluation is hysteroscopy, since it enables direct visualization of the uterine cavity and its relevant pathological disorders as well as the treatment of any detected abnormality, unlike the other indirect and purely diagnostic techniques, i.e. transvaginal sonography (TVS), hysterosalpingography (HSG) and saline infusion/gel instillation sonography (SIS/GIS) (Bettocchi *et al.*, 2002; Bakour *et al.*, 2006; Sagiv *et al.*, 2006; Di Spiezio Sardo *et al.*, 2010). Nevertheless, the use of hysteroscopy as a routine procedure in the infertility work-up is still under debate and there is no consensus on its efficacy and effectiveness in improving the prognosis of infertile couples.

The NICE guidelines on fertility assessment and treatment state that women should not be offered hysteroscopy on its own as part of the initial investigation unless clinically indicated, because the effectiveness of this technique on improving reproductive outcome has not been established (NICE, 2013).

On the other hand, the current evidence is giving an increasing attention to the 'time to pregnancy', already defined as 'an essential concept in human reproduction' (te Velde *et al.*, 2000). The prolonged time to pregnancy is becoming a crucial issue in the infertility work-up due to the dramatic increase in the mean age of women who attempt

spontaneous conception and ART treatments. This social phenomenon has to be given consideration in light of the relevant acceleration of ovarian aging as well as the increase in the aneuploidy rates above 35 years of age (Munné *et al.*, 2012).

In this regard, physicians are evaluating how to personalize diagnostic algorithms and treatment protocols for specific subgroups of 'low-prognosis' patients (Alviggi *et al.*, 2009, 2012).

The concept of the 'patient tailored approach' and the increasing interest and clinical relevance in shortening time to pregnancy clearly explain why fertility specialists need to improve each single detail in order to improve patients' success rate.

As a result, the scientific community has been re-evaluating the clinical relevance of hysteroscopy in the diagnosis and treatment of uterine factors and its role in the infertility work-up, thanks to its potential capability to improve reproductive outcomes and reduce time to pregnancy.

A Cochrane review (Bosteels *et al.*, 2013) assessed the effects of operative hysteroscopy on pregnancy rate compared with no intervention in women with otherwise unexplained infertility prior to intrauterine insemination (IUI), standard IVF or ICSI. Three other systematic reviews (El-Toukhy *et al.*, 2008; Bosteels *et al.*, 2010; Potdar *et al.*, 2012) assessed the effect of diagnostic and/or operative hysteroscopy on the reproductive outcome in women having their first or a subsequent IVF/ICSI attempt. More recently, the systematic review of Pundir *et al.* (2014) assessed the use of routine hysteroscopy prior to the first IVF/ICSI cycle.

All these authors were faced with poor available evidence, consisting of a few efficacy (explanatory) studies and a total absence of effectiveness (pragmatic) trials: While the former determine whether an intervention produces the expected result in a select group of patients treated under ideal conditions, the latter measure the degree of beneficial effect in the 'real-world' of clinical practice.

Although efficacy and effectiveness exist on a continuum, the generalizability of the trial results depends largely on the viewpoint of the observer and the conditions under investigation. As a consequence, any healthcare intervention is rarely recommended when pragmatic trials are missing. Under these circumstances, since the available trials assessed the efficacy of hysteroscopy in selected populations of infertile women only under the 'artificial' environment of the trial, none of the authors were able to draw definitive conclusions about the role of diagnostic and operative hysteroscopy in the infertility work-up.

Objectives

Our systematic review and meta-analysis was designed with a pragmatic attitude, to try to demonstrate whether the systematic execution of diagnostic and/or operative hysteroscopy might contribute to improved reproductive outcomes in infertile couples at different stages of their diagnostic–therapeutic work-up.

With this aim in mind, we combined the results of all the available randomized controlled trials (RCTs) assessing the impact on reproductive outcomes first of the systematic execution of hysteroscopy (diagnostic and possibly operative) in infertile women without suspected intrauterine cavity abnormalities (at any stage of the diagnostic work-up but prior to the first attempt of standard IVF or ICSI, or after one or more failed attempts of IVF/ICSI), and second of operative hysteroscopy in infertile women diagnosed with intrauterine abnormalities.

Methods

Inclusion criteria

Types of studies

All studies had to be RCTs.

Patients

All infertile women, with or without uterine cavity abnormalities, diagnosed at ultrasonography (US), HSG or SIS/GIS, and either enrolled during the basic infertility work-up (including IUI) and before being a candidate for any ART, or undergoing the first attempt of IVF/ICSI or undergone one or more failed attempts of IVF/ICSI.

Types of interventions

Experimental intervention: diagnostic or operative hysteroscopy performed during the initial infertility work-up or prior to the first or subsequent ART attempts (IVF/ICSI).

Control intervention: initial infertility work-up without hysteroscopy; IVF or ICSI attempt without prior diagnostic or operative hysteroscopy; diagnostic hysteroscopy alone.

Types of outcomes

Primary outcomes: Live birth rate (LBR), defined as the delivery of a live fetus after 20 complete weeks of gestation, resulting in at least one live baby being born. The delivery of a singleton, twins or births resulting from a multiple pregnancy was counted as one live birth (Zegers-Hochschild *et al.*, 2009). *Secondary outcomes*: clinical pregnancy rate, defined as a pregnancy diagnosed by US visualization of one or more gestational sacs or definitive clinical signs of pregnancy (Zegers-Hochschild *et al.*, 2009); miscarriage rate, defined as the spontaneous loss of a clinical pregnancy before 20 complete weeks of gestation; procedure-related complications, defined as any complication due to hysteroscopy.

Search methods for the identification of studies

The following databases were searched: PubMed (to June 2014), Embase (1974 to June 2014), the Cochrane Library (Cochrane Reviews and Trials databases) and The Clinical Trials registry (http://clinicaltrials.gov/) to June 2014. For the search strategies, we combined Medical Subject Headings terms (MeSH for PubMed and the Cochrane Library, Emtree for Embase), and keyword terms and phrases (PubMed electronic search strategy [infertility* and hysteroscopy*, and 'pregnancy rate']), or ('Infertility, Female' [Mesh] and 'Hysteroscopy' [Mesh] and 'Pregnancy Rate' [Mesh]). These terms for the strategy were modified according to Embase and the Cochrane Library systems. Moreover, the reference list of already published systematic reviews and retrieved primary studies was inspected. No language or year restrictions were applied to all the searches.

Study selection and data extraction

Two authors (V.P., S.M.) independently screened titles and abstracts of studies obtained by the search strategy. The full text of each potentially relevant study was obtained and assessed for inclusion independently by the two authors. They also independently extracted data from the included studies.

Two other authors (A.D.S.S., M.S.) independently reviewed the selection and data extraction process. The results were compared, and any disagreement discussed and resolved by consensus. When insufficient information was reported in the available papers, we wrote to the authors to ask for further data.

Assessment of risk of bias in included studies

The assessment of risk of bias for RCTs in this review was independently performed by two authors (V.P., S.M.), using the criteria recommended by the Cochrane Handbook (Higgins et al., 2011). The recommended approach for assessing the risk of bias in studies included in the Cochrane Review is a two-part tool, addressing seven specific domains, namely sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessor (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other sources of bias. The first part of the tool involves describing what was reported to have happened in the study. The second part of the tool involves assigning a judgment relating to the risk of bias for that entry, in terms of low, high, or unclear risk.

Grading of evidence

We also assessed the overall quality of the evidence for the primary outcome using the GRADE approach (GRADE working group, 2004; Schünemann et al., 2006; Guyatt et al., 2008; Guyatt et al., 2011), which takes into account issues not only related to internal validity but also to external validity, such as directness of results (i.e. the correspondence between the population, the intervention or the outcomes measured in the studies actually found and those under consideration in our systematic review), inconsistency of the results between the included studies, imprecision of the results due to small sample size or very few studies included, publication or outcome reporting bias.

Data synthesis and subgroup analysis

Dichotomous outcomes were analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by their confidence interval (CI). Continuous outcomes were analysed by calculating the mean differences or standard mean differences with 95% CI.

The outcome measures from the individual trials were combined through meta-analysis where possible (comparability of intervention and outcomes between trials), using the random effect model because some heterogeneity between included trials was expected for the types of participants, settings and treatments administered. Heterogeneity was analysed by means of the I^2 statistic and χ^2 tests for heterogeneity. The cut points were $I^2 > 50\%$ and P of the χ^2 test < 0.1.

We intended to use funnel plots (plots of the effect estimate from each study against the standard error) to assess the potential for bias related to the size of the trials, which could indicate possible publication bias if a sufficient number of studies (i.e. at least 10 studies) were included, but not enough studies were included. In the final overall meta-analysis, only seven of the nine selected studies were included.

Two main comparisons were made. The first comparison aimed to assess the efficacy of diagnostic, and in certain cases operative, hysteroscopy in improving the LBR and pregnancy rate during the infertility work-up when compared with no hysteroscopy in infertile women without suspected uterine cavity abnormalities diagnosed by US, HSG, SIS/GIS. For this comparison, the following subgroup analyses were performed: diagnostic or operative hysteroscopy at any stage of the infertility work-up (including IUI), but prior to the first IVF/ICSI attempt; diagnostic or operative hysteroscopy in women with one or more implantation failures after IVF/ICSI.

The second comparison aimed to assess the efficacy of operative hysteroscopy in improving the LBR and pregnancy rate when compared with only diagnostic hysteroscopy in women previously diagnosed with intrauterine abnormalities at US, HSG, SIS/GIS.

Statistical analysis was undertaken using Review Manager Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

From the bibliographic searches, a total of 588 records were retrieved after removing duplicates. Nineteen studies were initially selected in full text as being potentially relevant (Demirol and Gurgan, 2004; Perez-Medina et al., 2005; Casini et al., 2006; HaEmek Medical Center, 2006; Rama Raju et al., 2006; Colacurci et al., 2007; Pabuccu et al., 2008; van Dongen et al., 2008; El-Toukhy et al., 2009; Shokeir et al., 2010; Tonguc et al., 2010; El-Nashar and Nasr, 2011; Aghahosseini et al., 2012; El-Khayat, 2012; Hvidovre University Hospital, 2012; Shawki et al., 2012; Shohayeb and El-Khayat, 2012; Smit et al., 2012; National and Kapodistrian University of Athens, 2013). Seven studies were subsequently excluded:

(i) Shokeir et al. (2010) because it was retracted at the request of the editor as it duplicated parts of a paper on a different topic, which had already appeared in another journal;
(ii) Colacurci et al. (2007) because the study compared two methods of hysteroscopic treatment of uterine septa in a mixed population with infertility and recurrent pregnancy loss;
(iii) van Dongen et al. (2008) because the study compared conventional hysteroscopy using a resectoscope with hysteroscopic morcellation for the removal of polyps or fibroids in a mixed population of women suffering from infertility or other gynaecological conditions;
(iv) Pabuccu et al. (2008) because both groups within the study received office hysteroscopy, and it compared early second-look office hysteroscopic adhesiolysis after hysteroscopic adhesiolysis and Intrauterine Device insertion with no early second-look operative hysteroscopy;
(v) Tonguc et al. (2010) because all groups received hysteroscopic lysis of intrauterine adhesions and the study assessed the efficacy of adjunctive therapy in a mixed population of women with infertility and/or recurrent miscarriage;
(vi) HaEmek Medical Center (2006) because it was the protocol of an on-going study, for which the recruitment status was unknown and the information had not been updated since August 2006;
(vii) Shohayeb and El-Khayat (2012) because it assessed the efficacy of endometrial scraping not performed hysteroscopically.

Five studies were classified among the on-going trials and therefore not included in this review (El-Toukhy et al., 2009; El-Khayat, 2012; Hvidovre University Hospital, 2012; Smit et al., 2012; National and Kapodistrian University of Athens, 2013).

Two further studies, whose results became available after our literature search, were included because they were relevant to our review:

(a) A RCT published online in January 2015 (Elsetohy et al., 2015) and the preliminary results of the multicentre TROPHY study (El-Toukhy et al., 2014) presented at the European Society of Human Reproduction and Embryology (ESHRE) congress 2014.

In the end, nine studies with a total of 2976 participants were included in the review and seven studies were included in the meta-analysis (see Fig. 1).

Characteristics of included studies

For three studies, only information reported in conference proceeding abstracts were available (El-Nashar and Nasr, 2011; Aghahosseini et al., 2012; El-Toukhy et al., 2014). The authors were contacted to provide the missing data.

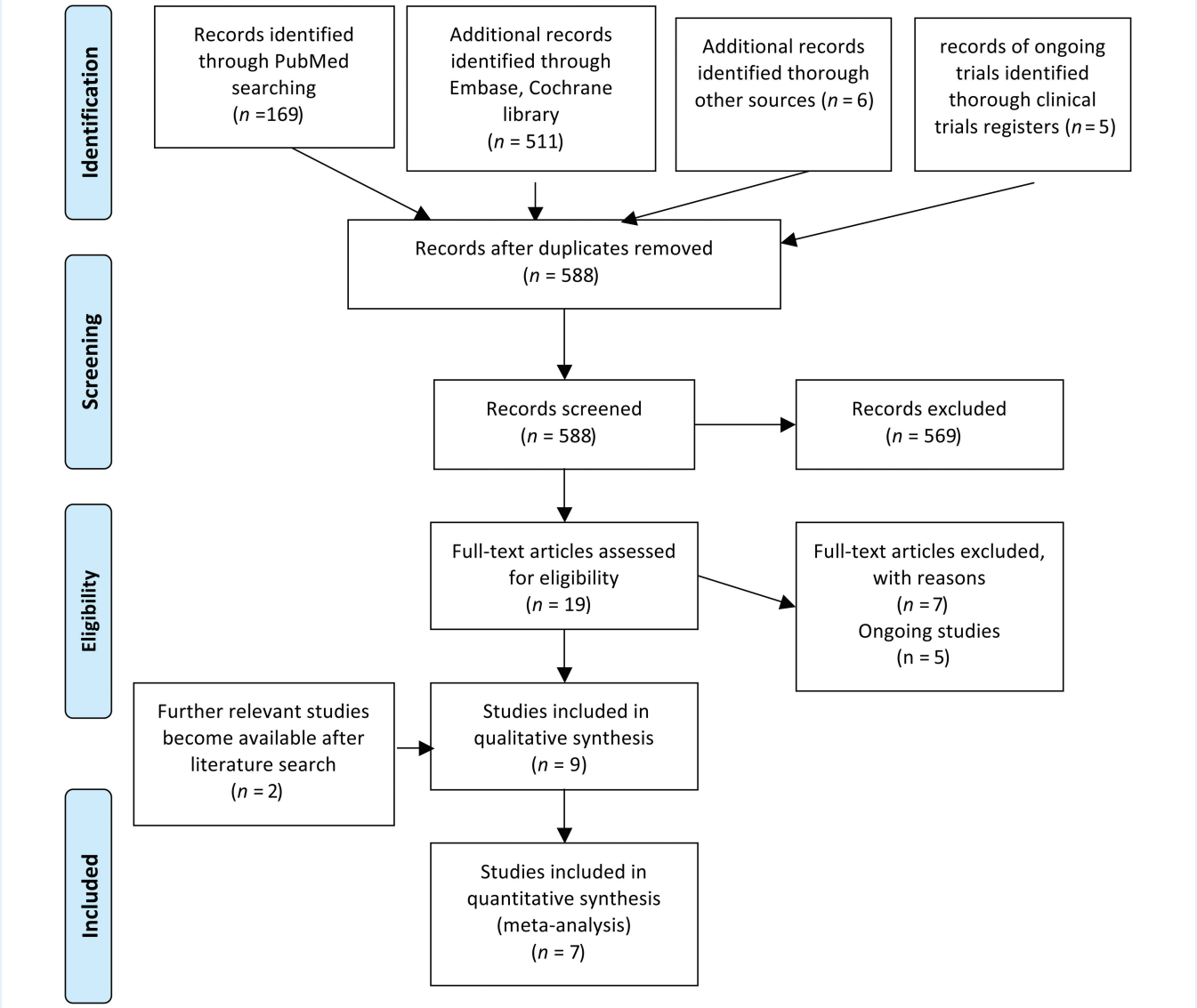

Figure 1 PRISMA flow chart for a review of the efficacy of hysteroscopy in improving reproductive outcome in infertile couples.

Types of patients and interventions compared

One study (Casini *et al.*, 2006) included women affected by uterine fibroids and otherwise unexplained infertility who had been trying to conceive for at least 1 year without success, but who had not received IVF/ICSI in the past and were not candidates for a future attempt. Patients in the experimental group underwent hysteroscopic resection of fibroids and the control group did not. Both were then invited to have regular pregnancy-oriented intercourse. Only the data of patients with submucous fibroids with or without intramural fibroids were considered in the present review ($n = 52$).

One study (Perez-Medina *et al.*, 2005) included infertile women affected by endometrial polyps and candidates for their first IUI. The authors compared hysteroscopic polypectomy with diagnostic hysteroscopy and polyp biopsy only.

Two studies included infertile women who were candidates for their first IVF/ICSI (El-Nashar and Nasr, 2011; Elsetohy *et al.*, 2015). Four studies (Demirol and Gurgan, 2004; Rama Raju *et al.*, 2006; Aghahosseini *et al.*, 2012; El-Toukhy *et al.*, 2014) included infertile women with two or more failed IVF/ICSI cycles and unsuspected or no uterine cavity abnormalities. One study (Shawki *et al.*, 2012) included both women candidates for their first IVF/ICSI and women with one or more failed IVF/ICSI cycles (see Table I).

These studies compared women who underwent hysteroscopy with correction of any detected intrauterine abnormalities, if encountered, with controls who started their IVF/ICSI cycles without undergoing hysteroscopy. The definition of failed IVF/ICSI was the same in all the included studies [i.e. the absence of implantation (itself defined by a negative serum HCG 14 days after oocyte collection) after transfer of two or more good-quality embryos for each IVF/ICSI cycle)].

Timing of hysteroscopy

The exact timing of hysteroscopy before any ART attempt was not known for two studies (Shawki *et al.*, 2012; El-Toukhy *et al.*, 2014). In

Table I Characteristics of nine studies included in a systematic review of the efficacy of hysteroscopy in improving reproductive outcomes in infertile couples.

Author, publication year	Country	Participants (*n*) and main inclusion criteria	Intervention	Control	Outcomes
Aghahosseini *et al.* (2012)	Iran	353 undergoing ICSI who have had two or more than two implantation failures with: - unsuspected or no uterine cavity abnormalities - normal hysterosalpingogram - no history of hysteroscopy in the last 2 months - age <38 years	Hysteroscopy prior to a subsequent ICSI attempt ($n = 142$); timing of hysteroscopy: the cycle before ICSI	Immediate ICSI without prior hysteroscopy ($n = 211$)	Clinical pregnancy rate diagnosed by the detection of fetal heart rate Live birth rate
Casini *et al.* (2006)	Italy	181 women affected by uterine fibroids and without all other causes of infertility who had been trying to conceive for at least 1 year without success 52 had submucosal fibroids, 45 had intramural fibroids, 11 had subserosal fibroids, 42 had a mix of submucosal–intramural and 31 patients had a mix of intramural–subserosal fibroids Mean age 31.6 years Mean years of infertility: 1.7	Hysteroscopic surgery to remove the fibroids ($n = 92$). Patients were suggested to abstain from having sexual intercourse for 3 months and then to start having regular fertility-oriented intercourse	No treatment ($n = 78$). Patients were suggested to immediately start having regular fertility-oriented intercourse (intercourse during the 6-day fertile interval ending on the day of ovulation) The 11 patients with subserosal fibroids were not randomized to treatment because there was little indication to surgery	Clinical pregnancy (diagnosed by visualization of an embryo with cardiac activity at 6–7 weeks of pregnancy) Miscarriage rate (defined as clinical loss of an intrauterine pregnancy between the 7th and 12th weeks of gestation)
Demirol and Gurgan (2004)	Turkey	421 patients with primary infertility and two or more failed IVF cycles with: - unsuspected or no uterine cavity abnormalities - normal hysterosalpingogram Infertility factors: - Ovulatory factor: $n = 140$ - Male factor: $n = 112$ - Unexplained: $n = 169$ Mean age: 32 years Mean years of infertility: 6.5	Office hysteroscopic evaluation of the uterine cavity and cervix before commencing controlled ovarian stimulation for IVF treatment. All office hysteroscopies performed 2–6 months after the last failed IVF cycles intrauterine lesions diagnosed were operated during the office procedure 156 patients had normal hysteroscopic findings, whereas 56 had abnormal office hysteroscopy findings, which were corrected at the same time All IVF treatments were carried out on the menstrual cycles after office hysteroscopies ($n = 210$)	No office hysteroscopic evaluation of the uterine cavity and cervix before commencing controlled ovarian stimulation for IVF treatment ($n = 211$)	Clinical pregnancy confirmed by transvaginal US at 6–7 weeks of gestation Miscarriage rate defined as first trimester abortion

Elsetohy *et al.* (2015)	Egypt	203 women randomized; 193 completed the study and were analysed with primary ($n = 123$) or secondary ($n = 70$) infertility scheduled for a first IVF/ICSI treatment cycle with: - no abnormality detected, apart from intramural myomas without uterine cavity deformity - Infertility factors*: • Ovarian factor ($n = 32$) • Male factor ($n = 99$) • Tubal factor ($n = 52$) • Unexplained ($n = 40$) *More than one cause of infertility present in some women - Mean age: 30.5 years - Mean years of infertility: 5.8	Hysteroscopic examination in the early–mid-follicular phase of a menstrual cycle. If any intrauterine abnormality (endometrial polyps, polypoidal endometrium septate uterus, adhesions and chronic or acute endometritis, and submucous myomata) was detected, therapeutic hysteroscopy was performed in the same hysteroscopy session or scheduled for operative procedures later. ICSI performed within 3 months of hysteroscopic examination ($n = 102$ randomized,97 analysed)	ICSI without hysteroscopy ($n = 101$randomised, 96 analysed)	Clinical pregnancy (diagnosed by pregnancy test 2 weeks after embryo transfer and positive test confirmed by an ultrasound 1 week later)
El-Nashar and Nasr (2011)	Egypt	124 women with unexplained infertility after carrying out the basic investigations for husband and wife, scheduled to start their first ICSI cycle. Mean age: 28 ± 2.6 (SD) years Mean years of infertility: 3 ± 1.7 (SD) years	Hysteroscopy with directed biopsy and correction of any intrauterine abnormalities encountered Exact timing of hysteroscopy before ICSI not specified ($n = 62$)	ICSI cycle without undergoing a hysteroscopy ($n = 62$)	Clinical pregnancy (diagnosed when fetal heartbeats were visualized on transvaginal US)
El-Toukhy *et al.* (2014)	UK, Italy, Belgium, Czech Republic	719 infertile women younger than 38 years, with two to four failed IVF cycles and planned a further IVF/ICSI cycle Mean age: 32.6 years Man years of infertility: 4.25	Outpatient hysteroscopy using a 3.7 mm continuous-flow hysteroscope without sedation before starting the IVF cycle. Exact timing of hysteroscopy before IVF not reported ($n = 367$)	IVF cycle without prior hysteroscopy ($n = 352$)	Clinical pregnancy (diagnosed by ultrasound scan at 6–7 weeks of gestation)
Perez-Medina *et al.* (2005)	Spain	215 infertile women with at least 24 months of sterility, with a sonographic diagnosis of endometrial polyps and who were candidates for IUIOther infertility factors*: - Ovulatory factors ($n = 71$) - Cervical factor ($n = 24$) - Endometriosis ($n = 23$) - Male factor ($n = 46$) - Unexplained ($n = 105$) *More than one cause of infertility present in some womenMean age: 38.5Mean years of infertility: not reported	Hysteroscopic polypectomy Women were scheduled to receive four cycles of IUI; the first IUI planned for three cycles after hysteroscopy ($n = 107$)	Endometrial polyps were not extracted during diagnostic hysteroscopy and polyp biopsy was performed Women were scheduled to receive four cycles of IUI; the first IUI planned for three cycles after hysteroscopy ($n = 108$)	Clinical pregnancy (diagnosed by pregnancy test and transvaginal US)

Continued

Table I *Continued*

Author, publication year	Country	Participants (*n*) and main inclusion criteria	Intervention	Control	Outcomes
Rama Raju *et al.* (2006)	India	520 patients with two or more failed IVF/ICSI cycles with: - Primary infertility • 61% female infertility (ovarian and/or tubal factor) • 31.5% male infertility • 7.5% combined male and female factor - Unsuspected or no uterine cavity abnormalities (normal appearance of the uterine cavity on HSG) Mean age: 28 years Mean years of infertility: 7 years	Office hysteroscopy prior to a subsequent IVF attempt ($n = 255$): 160 patients had normal hysteroscopic findings, whereas 95 had abnormal office hysteroscopy findings, which were corrected at the same time After hysteroscopy, ovarian stimulation was initiated on Day 21 of the cycle	Immediate IVF without prior hysteroscopy ($n = 265$)	Clinical pregnancy (visualization of fetal heart pulsation by TVS Miscarriage rate (no definition provided) Live birth rate
Shawki *et al.* (2012)	Egypt	240 infertile women randomized; 215 completed the study and included in the analysis (132: primary infertility; 83 secondary infertility) 116 were candidate to a first ICSI and 99 had one or more failed ICSI. All patients had: - unsuspected or no uterine cavity abnormalities (normal HSG and TVS) - Infertility factors: • Ovarian factors ($n = 58$) • Tubal factor ($n = 59$) • Male factor ($n = 49$) • Unexplained ($n = 44$) • Others ($n = 5$) Mean age: 32 years Mean years of infertility: 8 years	ICSI after performing office hysteroscopy using vaginoscopic technique Abnormal findings were recorded and treated according to the standard protocol of each pathology specific for the centre Exact timing of hysteroscopy prior to ovarian stimulation and embryo transfer not specified ($n = 120$ randomized, 110 analysed)	ICSI without office hysteroscopy ($n = 120$ randomized; $n = 105$ analysed)	Clinical pregnancy defined as case who had sonographic evidence of intrauterine pregnancy with positive fetal cardiac activity LBR (date obtained from the author)

Demirol and Gurgan (2004) and Aghahosseini *et al.* (2012), all IVF/ICSI treatments were carried out on the menstrual cycles immediately after hysteroscopies. In Rama Raju *et al.* (2006), ovarian stimulation was initiated on Day 21 of the cycle after hysteroscopy. In Elsetohy *et al.* (2015), IVF/ICSI was performed within 3 months of hysteroscopic examination. In El-Nashar and Nasr (2011), hysteroscopy was performed 3 months before the ART cycle. In Perez-Medina *et al.* (2005), the first IUI was planned for three cycles after hysteroscopy. In Casini *et al.* (2006), regular fertility-oriented intercourse was recommended 3 months after hysteroscopic surgery and immediately after diagnostic hysteroscopy.

Country

Three studies were conducted in Egypt and one each in Spain, Italy, India, Turkey and Iran. One was a multicentre study conducted in seven centres in the UK, Italy, Belgium and the Czech Republic. For a detailed description of the included studies, see Table I.

Risk of bias in included studies

All but two studies (El-Nashar and Nasr, 2011; Aghahosseini *et al.*, 2012) had a low risk of selection bias because they used an adequate method of random sequence generation. In two studies (El-Nashar and Nasr, 2011; Aghahosseini *et al.*, 2012), the method was not reported, so they were judged as being of unclear risk of bias. Three studies were judged to be at low risk of selection bias for the use of an adequate method of allocation concealment (Perez-Medina *et al.*, 2005; Shawki *et al.*, 2012; El-Toukhy *et al.*, 2014). The other studies were judged as being of unclear risk because the information was not reported. Blinding of personnel and participants was not possible for the types of intervention compared; nevertheless, five studies (Demirol and Gurgan, 2004; Perez-Medina *et al.*, 2005; Rama Raju *et al.*, 2006; Shawki *et al.*, 2012; Elsetohy *et al.*, 2015) were judged at low risk of performance bias because the authors reported that the same protocol was followed for both groups for other treatments received. One study (Casini *et al.*, 2006) was judged at high risk of performance bias because patients who did not receive surgery were asked to immediately start regular fertility-oriented intercourse, whereas patients who received surgery were advised to abstain from sexual intercourse for 3 months. The other studies were judged at unclear risk of performance bias because not enough information was provided in the articles about the similarity of other treatments received. None of the studies reported whether the outcome assessors were blinded; nevertheless, all studies were judged as being at low risk for detection bias because the outcomes were objective and unlikely to be biased by a lack of blinding. All but two studies (El-Nashar and Nasr, 2011; Aghahosseini *et al.*, 2012) were judged to be at low risk of attrition bias because there were no, or very few, participants who were withdrawn from the studies, there was a balance between groups, and the reasons for withdrawal were always reported. In the study of El-Toukhy *et al.* (2014), results from 3.5% of patients were not given, and the reasons for these missing data and allocation groups of the missing patients were not reported. However, the percentage of missing data was very small and unlikely to have biased the results. Aghahosseini *et al.* (2012) and El-Nashar and Nasr (2011) were judged at unclear risk of attrition bias because no information was reported. Four studies were judged at low risk of selective outcome reporting bias because the results of all the relevant outcomes (LBR, clinical pregnancy rate, miscarriage rate) were reported (Rama Raju *et al.*, 2006; Aghahosseini *et al.*, 2012), or because the clinical pregnancy rate and miscarriage rate were reported (Demirol and Gurgan, 2004; Casini *et al.*, 2006). The other studies were judged at high risk of selective outcome reporting because neither miscarriage rate nor LBR were reported (see Table II and Fig. 2).

Effect of intervention

Live birth rate

Only three studies assessed this outcome.

Comparison 1: Hysteroscopy versus no hysteroscopy in the infertility work-up. Three studies with 1088 participants found a significantly higher LBR in the hysteroscopy group (RR1.48, 95% CI 1.20–1.81, I^2= 0%, $P = 0.82$). One study reported separate results for women with previous implantation failure and women undergoing the first IVF/ICSI attempt. In the subgroup analysis of 972 women with implantation failure (one or more) after IVF/ICSI we found a higher LBR (RR 1.48, 95% CI 1.19–1.85, $I^2 = 0\%$, $P = 0.64$), but not in the subgroup of 116 participants where hysteroscopy was performed before the first IVF/ICSI attempt (RR 1.44, 95% CI 0.83–2.48) (Fig. 3). Quality of evidence was judged as very low (see Fig. 4).

Comparison 2: Operative hysteroscopy for fibroid or polyp removal versus diagnostic hysteroscopy. None of the included studies assessed this outcome.

Pregnancy rate

Comparison 1: Seven studies with 2545 participants were included. The overall results favoured hysteroscopy (RR 1.45, 95% CI 1.26–1.67, $I^2 =$ 38%, $P = 0.12$). These results were confirmed in the subgroup analysis of five of the studies with 2112 participants, which included only women with implantation failure after IVF/ICSI (RR 1.41, 95% CI 1.14–1.75, I^2= 62%, $P = 0.03$), and in the three remaining studies with 433 participants where hysteroscopy was performed before the first IVF/ICSI attempt (RR 1.55, 95% CI 1.26–1.91, $I^2 = 0\%$, $P = 0.96$]; see Fig. 5). Quality of evidence was judged as moderate (see Fig. 4).

Comparison 2: Two studies with 256 participants were included. The overall results favoured operative hysteroscopy (RR 2.13, 95% CI 1.56–2.92, $I^2 = 0\%$, $P = 0.43$; see Fig. 6). Quality of evidence was judged as low (see Fig. 7).

Miscarriage rate

Only three studies assessed this outcome.

Comparison 1: Two studies with 941 participants which included only women with two or more failed IVF/ICSI were included. The overall results did not find a significant difference (RR 1.25, 95% CI 0.70–2.21, $I^2 = 28\%$, $P = 0.24$; see Fig. 8). Quality of evidence was judged as low (see Fig. 4).

Comparison 2: Only one study with 52 patients was included. We did not find a significant difference in miscarriage rate between the two groups (RR 1.22, 95% CI 0.33–4.58). Quality of evidence was judged as very low (see Fig. 7).

Complications

None of the studies included in this review assessed complications. Only Demirol and Gurgan (2004) reported that, in all cases, diagnostic hysteroscopy and operative procedures were carried out with success

Table II Risk of bias in the nine studies included in the systematic review.

Authors, publication year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessor (detection bias)	Incomplete outcome data (attrition bias)	Selective outcome reporting (reporting bias)
Aghahosseini *et al.* (2012)	Unclear risk: information not reported	Unclear risk: information not reported	Unclear risk: blinding not possible; no detailed information provided about similarity of other treatment protocol	Low risk: objective outcome unlikely to be biased by lack of blinding	Unclear risk: information not reported	Low risk: all the prespecified outcomes reported
Casini *et al.* (2006)	Low risk: randomization table	Unclear risk: information not reported	High risk: blinding not possible. Patients without surgery asked to immediately start regular fertility-oriented intercourse. Patients with surgery suggested to abstain from sexual intercourse for 3 months	Low risk: objective outcome unlikely to be biased by lack of blinding	Low risk: no withdrawal from the study	Low risk: LBR not reported, but miscarriage rate reported
Demirol and Gurgan (2004)	Low risk: computer-generated random numbers	Unclear risk: information not reported	Low risk: blinding not possible. Same protocol followed for both group for other treatment	Low risk: objective outcome unlikely to be biased by lack of blinding	Low risk: three patients (0.7%) excluded from the analysis (two from experimental group, one from control group) due to failed embryo transfer, poor ovarian response, poorly graded embryos	Low risk: LBR not reported, but miscarriage rate reported
Elsetohy *et al.* (2015)	Low risk: computer-generated random numbers	Unclear risk: information not reported	Low risk: blinding not possible. Same protocol followed for both group for other treatment	Low risk: objective outcome unlikely to be biased by lack of blinding	Low risk: 10 patients (5%) were lost from the study, because of lost at follow-up during the induction of ICSI, balanced between groups	High risk: LBR and miscarriage rate not reported
El-Nashar and Nasr (2011)	Unclear risk: information not reported	Unclear risk: information not reported	Unclear risk: blinding not possible; no detailed information provided about similarity of other treatment protocol	Low risk: objective outcome unlikely to be biased by lack of blinding	Unclear risk: information not reported	High risk: LBR and miscarriage rate not reported
El-Toukhy *et al.* (2014)	Low risk: 'Minimization' method using a computer-based algorithm used to avoid chance imbalances in important stratification variables	Low risk: third party, distant, internet-based randomization	Unclear risk: blinding not possible; no detailed information provided about similarity of other treatment protocol	Low risk: objective outcome unlikely to be biased by lack of blinding	Low risk: results of 25 randomized patients (3.5%) not available yet; not reported to which group they were allocated	High risk: LBR and miscarriage rate not reported
Perez-Medina *et al.* (2005)	Low risk: computerized random number table	Low risk: opaque envelope technique	Low risk: blinding not possible. Same protocol followed for both group for other treatment	Low risk: objective outcome unlikely to be biased by lack of blinding	Low risk: 11 patients withdrawn from the study (5%), because lost to follow-up, polyp not confirmed and two pathologic reports of myoma balanced between groups	High risk: LBR and miscarriage rate not reported
Rama Raju *et al.* (2006)	Low risk: computer-generated random numbers	Unclear risk: information not reported	Low risk: blinding not possible. Same protocol followed for both group for other treatment	Low risk: objective outcome unlikely to be biased by lack of blinding	Low risk: five patients withdrawn from the study (1%), because poor quality of embryos balanced between groups	Low risk: all the prespecified outcomes reported
Shawki *et al.* (2012)	Low risk: computer-generated random numbers in blocks of 8	Low risk: sealed envelopes	Low risk: blinding not possible. Same protocol followed for both group for other treatment	Low risk: objective outcome unlikely to be biased by lack of blinding	Low risk: 25 patients withdrawn from the study (10%), because lost to follow-up, no fertilization, bad-quality embryos balanced between groups	High risk: LBR and miscarriage rate not reported

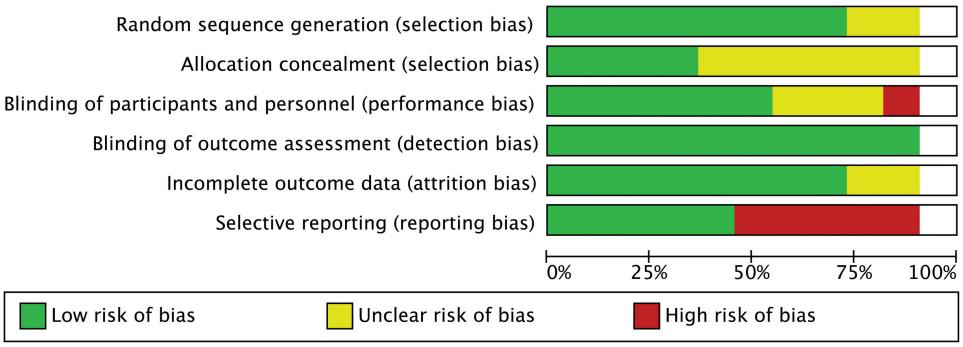

Figure 2 Risk of bias graph for the nine studies included in the systematic review: the authors' judgment about each risk of bias item presented as percentages across all studies.

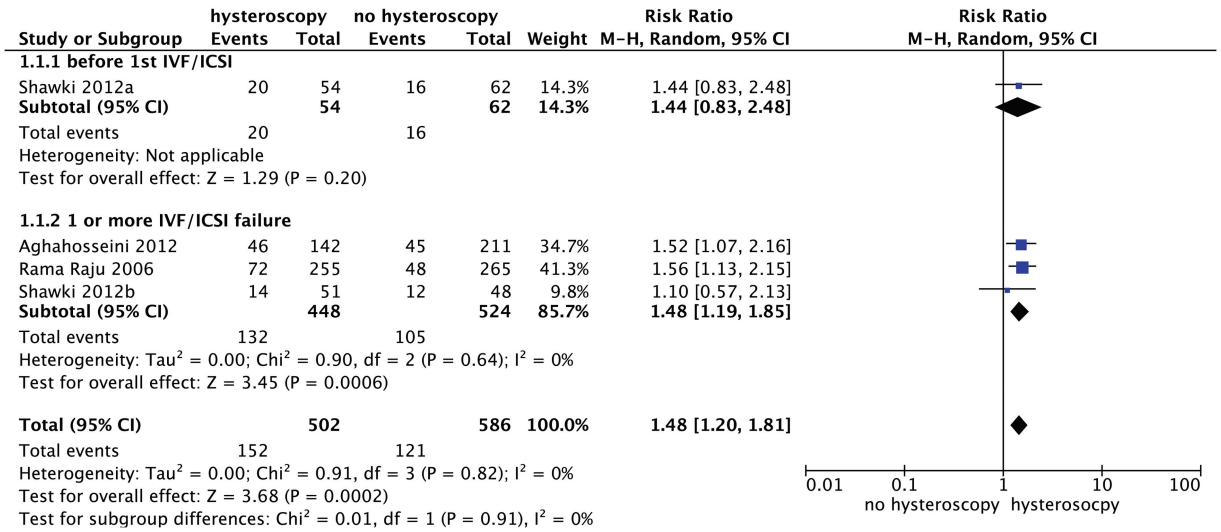

Figure 3 Women with previous implantation failure and women undergoing the first IVF/ICSI attempt. Hysteroscopy versus no hysteroscopy. Live birth rate.

without any particular difficulty. Most of the patients experienced mild pain resembling menstrual cramps, especially during the passage of the tip of the hysteroscope through the internal cervical ostium. Six patients had to undergo a repeated hysteroscopy due to unsatisfactory distension of the uterine cavity, all of which were successful.

Discussion

The current infertility work-up includes both diagnostic and therapeutic steps: in the first place, it includes the assessment of contributors to infertility and is based on specific investigations including tests of ovulation and tubal patency, as well as semen analysis. Subsequently, when indicated, pregnancy-oriented intercourse, induction of ovulation and IUI are attempted. The recourse to ART is reserved for those cases in which contributors to infertility cannot be overcome by previous work-up steps, or when previous therapeutic attempts have failed to achieve a pregnancy (NICE, 2013).

The evaluation of the uterine capacity for reproduction is an important step during infertility work-up, either during initial assessment or when any ART procedure is scheduled. In fact, intrauterine lesions are more common in infertile women, compromising spontaneous fertility as well as reducing pregnancy rates in assisted reproduction (Taylor and Gomel, 2008; Bosteels *et al.*, 2013; NICE, 2013).

In routine clinical practice, the first-line investigation tools for uterine factor are indirect imaging techniques such as TVS, HSG and SIS/GIS. In contrast, although hysteroscopy is considered to be the gold standard for the evaluation of the uterine cavity worldwide (Bettocchi *et al.*, 2002; Bakour *et al.*, 2006; Sagiv *et al.*, 2006; Di Spiezio Sardo *et al.*, 2010), as well as enabling the treatment of any detected intrauterine anomaly, it continues to be considered a second-line procedure for the uterine

Hysteroscopy compared to no hysteroscopy for infertility

Patient or population: women with . previous implantation failure and women undergoing the first IVF/ICSI attempt **Settings:**
Intervention: hysteroscopy
Comparison: no hysteroscopy

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk No hysteroscopy	Corresponding risk Hysteroscopy	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
live birth rate live foetus delivered after 20 complete weeks of gestation Follow-up: mean 9 months	**Study population**		**RR 1.48** (1.2 to 1.81)	1088 (3 studies)	⊕⊖⊖⊖ **very low**[1,2,3]	
	206 per 1000	**306 per 1000** (248 to 374)				
	Moderate					
	232 per 1000	**343 per 1000** (278 to 420)				
pregnancy rate pregnancy diagnosed by US visualization of one or more gestational sacs or definitive clinical signs of pregnancy Follow-up: 3-10 weeks	**Study population**		**RR 1.45** (1.26 to 1.67)	2545 (7 studies)	⊕⊕⊕⊖ **moderate**[4]	
	291 per 1000	**422 per 1000** (366 to 486)				
	Moderate					
	275 per 1000	**399 per 1000** (346 to 459)				
miscarriage rate spontaneous loss of a clinical pregnancy before 20 complete weeks of gestation Follow-up: mean 3 months	**Study population**		**RR 1.25** (0.7 to 2.21)	941 (2 studies)	⊕⊕⊖⊖ **low**[5,6]	
	71 per 1000	**89 per 1000** (50 to 158)				
	Moderate					
	69 per 1000	**86 per 1000** (48 to 152)				

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

CI: Confidence interval; **RR:** Risk 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] unclear allocation concealment in two studies
[2] three studies with 1088 participants
[3] live birth rate not reported in 5 studies despite long recruitment period
[4] unclear allocation concealment in 5 studies, unclear random sequence generation in 2 studies, unclear risk of performance bias in 3 studies, unclear risk of attrition bias in 2 studies
[5] unclear allocation concealment in both studies
[6] only two studies with 941 participants

Figure 4 Evidence profile: hysteroscopy compared with no hysteroscopy for women with previous implantation failure and women undergoing the first IVF/ICSI attempt.

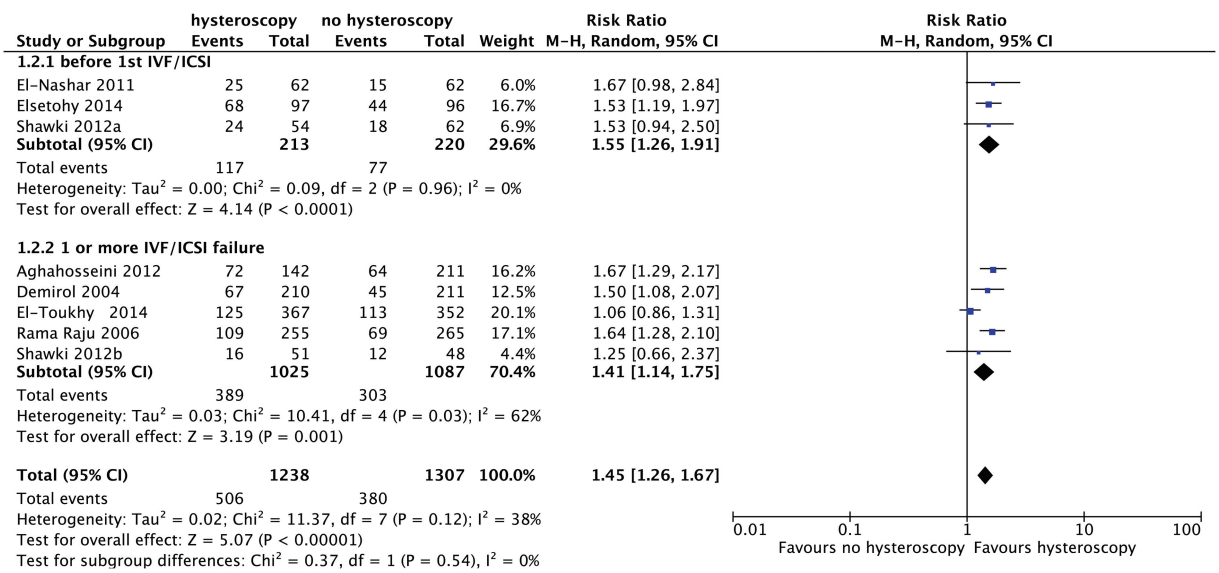

Figure 5 Women with previous implantation failure and women undergoing the first IVF/ICSI attempt. Hysteroscopy versus no hysteroscopy. Pregnancy rate.

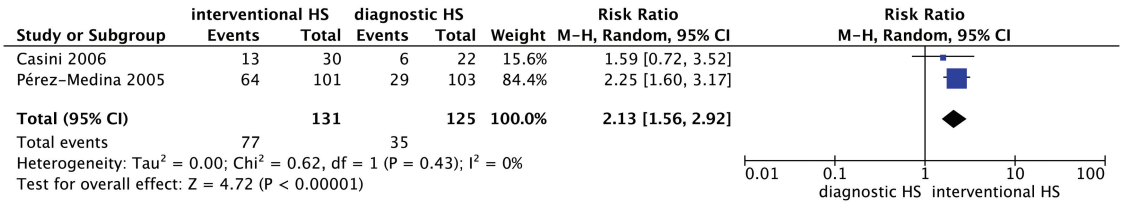

Figure 6 Infertile women affected by uterine fibroids or endometrial polyps. Operative versus diagnostic hysteroscopy. Pregnancy rate.

Operative compared to diagnostic hysteroscopy for infertility

Patient or population: Infertile women affected by uterine fibroids or endometrial polyps.
Settings:
Intervention: interventional
Comparison: diagnostic hysteroscopy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Diagnostic hysteroscopy	Corresponding risk Operative				
pregnancy rate Follow-up: 7-10 weeks	**Study population**		**RR 2.13** (1.56 to 2.92)	256 (2 studies)	⊕⊕⊖⊖ **low**[1,2]	
	280 per 1000	**596 per 1000** (437 to 818)				
	Moderate					
	277 per 1000	**590 per 1000** (432 to 809)				
miscarriage rate Follow-up: 12 weeks	**Study population**		**RR 1.22** (0.33 to 4.58)	52 (1 study)	⊕⊖⊖⊖ **very low**[1,3]	
	136 per 1000	**166 per 1000** (45 to 625)				
	Moderate					
	136 per 1000	**166 per 1000** (45 to 623)				

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

CI: Confidence interval; **RR:** Risk 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] 1 study with unclear allocation concealment, 1 study at high risk of performance bias
[2] only 2 studies with 256 participants
[3] only 1 study with 52 participants

Figure 7 Evidence profile: operative compared with diagnostic hysteroscopy for infertile women affected by uterine fibroids or endometrial polyps.

factor in infertile women (NICE, 2013); this being mainly related to its invasiveness and cost (The Practice Committee of the American Society for Reproductive Medicine, 2012).

However, recent evidence suggests that the role of hysteroscopy should be re-evaluated, since its execution at specific steps of the clinical work-up may improve the reproductive outcome of infertile couples (El-Toukhy *et al.*, 2008; Potdar *et al.*, 2012; Bosteels *et al.*, 2010, 2013; Pundir *et al.*, 2014).

Current data on this interesting topic remain limited by their paucity and fragmentation. In particular, it is not clear whether specific infertile populations may be more appropriate candidates for hysteroscopy and whether the timing of hysteroscopy could affect their reproductive prognosis. In other words, it is unclear at which specific step of the infertility work-up (e.g. at initial assessment, when an intrauterine abnormality is suspected by non-invasive methods, prior to timed intercourse/IUI, prior to first IVF/ICSI or after one or more failed IVF/ICSI, etc.) hysteroscopy should be performed in order to maximize its beneficial effects on reproductive outcomes.

The purpose of this systematic review and meta-analysis was to analyse the available evidence on this topic, in order to assess the correct indication and timing of diagnostic and operative hysteroscopy performed in different infertile populations (with and without intrauterine abnormalities).

Main findings

Nine RCTs with 2976 participants were included in the review. Four studies included infertile women with two or more failed IVF/ICSI cycles. Two studies included women who were candidates for their first IVF/ICSI. One study included both women candidates for their first IVF/ICSI and women with one or more failed IVF/ICSI cycles. Two studies included women affected by uterine fibroids and endometrial polyps, respectively, who had not previously received IVF/ICSI nor were candidates for future IVF/ICSI. LBR was the main measure of outcome. Pregnancy rate and miscarriage rate were the secondary outcomes.

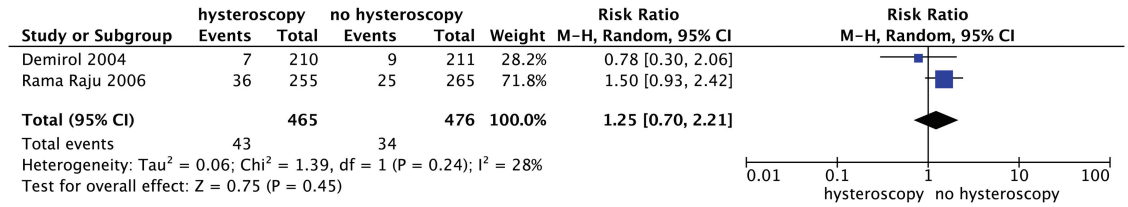

Figure 8 Women with previous implantation failure and women undergoing the first IVF/ICSI attempt. Hysteroscopy versus no hysteroscopy. Miscarriage rate.

Two main comparisons were performed. The first aimed at assessing the efficacy of systematic execution of diagnostic (and in some cases operative) hysteroscopy at any stage of the infertility work-up in women with normal US, HSG or SIS/GIS results in improving LBR and pregnancy rate when compared with no hysteroscopy, while the second was aimed at evaluating the efficacy of operative hysteroscopy in infertile women diagnosed with intrauterine abnormalities on the same outcomes when compared with diagnostic hysteroscopy.

Systematic execution of diagnostic (and possibly operative) hysteroscopy in infertile women without suspected intrauterine abnormalities

All the included studies evaluated the role of hysteroscopy before an IVF/ICSI (first attempt or subsequent ones) with a timing of one to three cycles preceding the ART attempt. No studies investigating the role of hysteroscopy in the initial assessment of the infertile couple were identified.

LBR was assessed only by three studies with 1088 participants. We found very low-quality evidence of a beneficial effect of hysteroscopy.

Pregnancy rate was assessed by seven studies. We found a moderate quality of evidence of a beneficial effect of hysteroscopy for women experiencing one or more implantation failures after IVF/ICSI and also for women undergoing their first IVF/ICSI.

Two reasons may be proposed to explain such results. First, hysteroscopy may reveal an unsuspected intrauterine abnormality in patients with a normal US, HSG or SIS/GIS, which may potentially hamper the implantation rate after IVF/ICSI. The treatment of these 'hidden' abnormalities may have contributed to the improved reproductive outcome in these patients. HSG or US have been proposed to be the primary diagnostic tools for uterine cavity abnormalities, but many studies (Gaglione *et al.*, 1996; Golan *et al.*, 1996; Brown *et al.*, 2000; Roma Dalfo *et al.*, 2004; Pundir and El Toukhy, 2010) have clearly demonstrated that they suffer from a lower sensitivity and specificity in comparison with hysteroscopy. HSG results may also change in different phases of the menstrual cycle, due to the variable growth of the endometrium. Moreover, air bubbles, mucus and menstrual debris could mimic filling defects, and can result from an excessive amount of contrast media in the uterus obliterating shadows caused by small endometrial lesions (Roma Dalfo *et al.*, 2004).

In comparison with hysteroscopy, bidimensional US was reported to have 84.5% sensitivity, 98.7% specificity, 98% positive predictive value and 89.2% negative predictive value (Pundir and El Toukhy, 2010). However, US might not diagnose submucosal fibroids in the presence of multiple fibroids or a large polyp from the hyperplasic endometrium. Bidimensional US may also not differentiate between congenital uterine malformations (Shawki *et al.*, 2012). Overall, comparative studies of HSG or US in the evaluation of uterine cavity abnormalities showed unacceptably high false negative rates, low positive predictive values and poor diagnostic accuracy values. Therefore, it appears that there will be abnormalities in approximately one-third of the patients where the HSG and/or US is interpreted as normal, which may cause a false reassurance and will actually lead to failure of conception (Gaglione *et al.*, 1996; Roma Dalfo *et al.*, 2004; Shawki *et al.*, 2012). Recent papers have reported that hysteroscopy allows the diagnosis of unsuspected intrauterine abnormalities in infertile women candidates for IVF in almost 50% of cases (Hinckley and Milki, 2004; Kasius *et al.*, 2009; Fatemi *et al.*, 2010; Karayalcin *et al.*, 2010). In our review, unsuspected abnormal uterine findings were diagnosed at office hysteroscopy in a percentage of women with normal findings at USG and/or HSG, varying from 9.7% (El-Nashar *et al.*, 2011) to 43.3% (Elsetohy *et al.*, 2015). A significant difference in the percentage of abnormal findings between women undergoing office hysteroscopy before the first IVF (9.7%, El-Nashar *et al.*, 2011; 43.3%, Elsetohy *et al.*, 2015) or after one or more IVF failure (26%, Demirol and Gurgan, 2004; 27%, El-Toukhy *et al.*, 2014; 37.25%, Rama Raju *et al.*, 2006) could not be detected.

Secondly, as already suggested by other authors, the benefit of hysteroscopy could extend beyond the treatment of intrauterine abnormalities. Several reasons have been proposed to explain such a benefit. First, irrigation of the cavity with saline may have a beneficial effect on implantation and pregnancy rates, since saline mechanically removes harmful anti-adhesive glycoprotein molecules on the endometrial surface involved in endometrial receptivity [i.e. cyclooxygenase-2 (COX-2), mucin-1 (MUC-1) and integrin αVβ3] (Takahashi *et al.*, 2000). Furthermore, the hysteroscopic diagnostic act itself may allow easier embryo transfer due to the passage of the tip of the hysteroscope through the cervical canal with the contemporaneous lysis of cervical adhesions, as well as the possibility of studying the course and morphology of the cervical canal, in order to make the embryo transfer procedures easier. All these have been considered as plausible explanations for the improved IVF outcome after hysteroscopy (Egbase *et al.*, 2000; Mansour and Aboulghar, 2002; Pabuccu *et al.*, 2005; Dhulkotia *et al.*, 2012; El-Toukhy *et al.*, 2012; Potdar *et al.*, 2012; Shohayeb and El-Khayat, 2012).

Other authors have investigated the role of mechanical endometrial injury in the cycle preceding or during ovarian stimulation for IVF in improving pregnancy rate. Indeed, mechanical manipulation of the endometrium may enhance receptivity by modulating the expression of gene encoding factors required for implantation, such as glycodelin A (Mirkin *et al.*, 2005), laminin alpha-4, integrin alpha-6 and matrix metalloproteinase-1 (Almog *et al.*, 2010).

In conclusion, the results of our first comparison indicate that hysteroscopic diagnosis and treatment of intrauterine abnormalities may improve pregnancy rates after ART, at least when compared with controls not receiving hysteroscopy. Pregnancy rates seem also to be improved in cases of normal hysteroscopy, suggesting that the simple performance of the procedure has a positive prognostic effect in achieving a subsequent pregnancy.

Only the study of El-Toukhy *et al.* (2014), a multicentre RCT of pre-IVF hysteroscopy in women with more than two but less than four IVF failures (the Trophy trial), was in disagreement with this trend, showing no significant improvement of IVF outcome in a population who underwent pre-IVF hysteroscopy compared with controls. However, this study was quite different from the others, including patients who had already undergone hysteroscopy before the previous IVF attempts, while the other trials included only patients who had never undergone hysteroscopy. This difference may have played a role in the reduced contribution of hysteroscopy in improving the reproductive outcome of the patients. In such cases, any uterine factor contributing to infertility may have been previously excluded (detected and treated) before undergoing hysteroscopy again. Furthermore, great heterogeneity in IVF outcomes, pre-IVF routine hysteroscopy and treatment of abnormalities was observed across the participating centres.

Operative hysteroscopy in infertile women with intrauterine abnormalities

All the studies included in this analysis evaluated the role of diagnostic and operative hysteroscopy in the initial assessment of infertile couples, being all the enrolled patients not candidates for ART. None of the studies included in this comparison assessed LBR.

We found low-quality evidence that clinical pregnancy rate increases in infertile women diagnosed with intracavitary abnormalities (i.e. endometrial polyps and submucous fibroids) detected at US, HSG or SIS/GIS, who underwent operative hysteroscopy compared with those who underwent diagnostic hysteroscopy only.

In particular, the study of Perez-Medina *et al.* (2005) found a clinical pregnancy rate of 51.4% in the polypectomy group after four IUI cycles, compared with 25.4% in the control group, corresponding with a number needed to treat (NNT) to achieve one additional pregnancy of 3 (NNT3 [95% CI 2–5]; Perez-Medina *et al.*, 2005; Bosteels *et al.*, 2010). Interestingly, a significant majority (65%) of all pregnancies in the polypectomy group occurred before starting the first IUI cycle, resulting in a spontaneous pregnancy rate of 29% in the polypectomy group versus 3% in the control group.

In the study of Casini *et al.* (2006), only the data of patients with submucous fibroids with or without intramural fibroids were used in the present review ($n = 52$). Among those who underwent myomectomy, the pregnancy rates obtained after fertility-oriented intercourse were 43.3% in cases of submucosal fibroid patients, and 40.0% in cases of submucosal–intramural fibroid patients.

These results confirm the hypotheses that intracavitary abnormalities, i.e. endometrial polyps (Shokeir *et al.*, 2004; Silberstein *et al.*, 2006; Taylor *et al.*, 2008; Yanaihara *et al.*, 2008) and submucous fibroids (Pritts, 2001; Somigliana *et al.*, 2007; Taylor *et al.*, 2008) may affect reproductive outcomes. The specific mechanisms of action through which each one of these intrauterine abnormalities disturbs this essential reproductive process are, as yet, poorly understood. Recent papers have shown that both endometrial polyps and submucosal myomas may adversely affect reproduction through a global decrease in endometrial HOX gene expression (Rackow and Taylor, 2010; Rackow *et al.*, 2011; Revel, 2012).

In summary, our results are in accordance with those of Bosteels et al. (2013), showing that the hysteroscopic removal of submucous fibroids may be beneficial in improving the chance of pregnancy in women with otherwise unexplained subfertility; the hysteroscopic removal of endometrial polyps suspected on ultrasound in women prior to IUI may increase the clinical pregnancy rate. Although encouraging, we are aware that these results have to be confirmed by further more robust studies.

We judged that, overall, the included studies could be considered at moderate risk of bias for concerns of internal validity; the major flaws consisting of the unclear risk of selection bias because of the lack of information about the allocation concealment methods (60% of the studies) and the high risk of selective outcome reporting (50% of the studies), because the studies did not report either miscarriage rate or LBR. Applying the GRADE approach, in the first comparison we judged that the quality of evidence was very low for LBR because of risk of bias, suspected outcome reporting bias and imprecision. Quality of evidence was moderate for pregnancy rate because of risk of bias, and it was low for miscarriage rate because of risk of bias and imprecision (Fig. 3). For the second comparison, the quality of evidence was low for pregnancy rate and very low for miscarriage rate because of risk of bias and imprecision (Fig. 7).

Limitations

We are aware that the current evidence lacks pragmatic (effectiveness) trials and, for this reason, our aim *a priori* was to assess the efficacy of hysteroscopy, as all included studies had been conducted in the 'artificial' setting of clinical trials. However, the populations included in our analysis, apart from sharing a common characteristic (the presence or absence of an intrauterine factor), were tremendously heterogeneous for several factors (i.e. main clinical characteristics, causes of infertility, timing of hysteroscopy, protocol of IVF/ICSI). This low methodological purity might represent a limitation of our paper, but the clinical diversity of the analysed study populations seems to have ensured a generalizability of our results, being that our infertile women were similar to those generally encountered in the real-world of clinical practice. Indeed, infertile couples are generally characterized by more than one cause of infertility, and multiple confounders in every centre usually affect the performance of the diagnostic and therapeutic work-up.

LBR is our primary outcome measure. While it represents the most relevant end-point in reproductive medicine, giving higher validity to our results, the percentage of papers reporting this end-point was relatively low, making it difficult for us to draw any definitive conclusions. However, the positive results in terms of increased clinical pregnancy rate are not of secondary value. Indeed, hysteroscopy is more likely to affect implantation and the early stages of pregnancy than later complications. In light of this consideration, clinical pregnancy rates may represent a more 'realistic' indicator of the hysteroscopy 'effect'.

Regarding the second comparison of our analysis, we are aware that pooling studies on polyps and fibroids could potentially limit the validity of our results. Indeed, pooling studies with different types of participants or interventions may affect the clinical plausibility of any result, regardless of any statistical heterogeneity. However, we think that this is not the case and we remain convinced about the validity of our choice for the following reasons: first, even if fibroids and polyps cause infertility by different pathogenic mechanism, both could be a cause of infertility treatable

by operative hysteroscopy. The latter data are enough for the purpose of our review that was to assess whether operative or diagnostic hysteroscopy improves live birth and/or pregnancy rate when performed in women with infertility for any or unknown reason; secondly, the emerging literature seems also to show that that endometrial polyps and submucosal myomas may adversely affect reproduction through the same pathogenic mechanism (Rackow and Taylor, 2010; Rackow *et al.*, 2011; Revel, 2012).

Another limitation of our review is that none of the included IVF studies were based on single embryo transfer policies. Such studies are strongly recommended, as they would better assess the role of hysteroscopy in terms of improved reproductive outcomes.

Conclusions

An increasing number of experimental and clinical studies have emphasized the importance of uterus and intrauterine pathology for spontaneous and post-ART fertility (Galliano *et al.*, 2015). Despite this, the endoscopic evaluation of the uterine environment in infertile couples remains understudied.

In our systematic review, we found that: there is no evidence about the role of hysteroscopy as a basic infertility evaluation tool; it is unclear whether hysteroscopy, performed before IVF, regardless of intrauterine abnormalities, improves LBR because of the very low-quality evidence; there is moderate quality evidence that hysteroscopy increases pregnancy rate if performed before IVF, regardless of intrauterine abnormalities; we found low-quality evidence that hysteroscopy may increase pregnancy rate when removing submucosal fibroids or endometrial polyps. No studies were found that looked at LBR when hysteroscopy was performed to remove submucosal fibroids or endometrial polyps.

Robust and high-quality RCTs are still needed before hysteroscopy can be regarded as a first-line procedure in all infertile women, especially during the initial clinical assessment of a couple where it could reduce the time-to-pregnancy and the need for ART.

Authors' roles

A. D.S.S. designed the study, selected studies for inclusion, reviewed the data extraction and risk of bias assessment and wrote the first draft of the manuscript; S.M. designed the study, extracted data from the included studies, assessed risk of bias, performed meta-analysis and wrote the first draft of the manuscript; V.P. performed the literature search; M.S. designed the study, selected studies for inclusion, reviewed the data extraction and wrote the first draft of the manuscript; C.D.C. designed the study, contacted all the authors of the included papers and critically revised the manuscript; C.A. gave a critical contribution in both data selection and manuscript revision; G.D.P. participated in the study design, gave a critical contribution in both data selection and manuscript revision; C.N. participated in the study design, structured the manuscript and wrote the manuscript; G.B. structured the manuscript, contacted all the authors of the included papers and gave a critical contribution in manuscript revision. All authors approved the final manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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