Hysteroscopy prior to the first IVF cycle: A systematic review and meta-analysis

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Abstract

This systematic review and meta-analysis investigated the use of routine hysteroscopy prior to starting the first IVF cycle on treatment outcome in asymptomatic women. Searches were conducted on MEDLINE, EMBASE, Cochrane Library, National Research Register and ISI Conference Proceedings. The main outcome measures were clinical pregnancy and live birth rates achieved in the index IVF cycle. One randomized and five non-randomized controlled studies including a total of 3179 participants were included comparing hysteroscopy with no intervention in the cycle preceding the first IVF cycle. There was a significantly higher clinical pregnancy rate (relative risk, RR, 1.44, 95% CI 1.08–1.92, \( P = 0.01 \)) and LBR (RR 1.30, 95% CI 1.00–1.67, \( P = 0.05 \)) in the subsequent IVF cycle in the hysteroscopy group. The number needed to treat after hysteroscopy to achieve one additional clinical pregnancy was 10 (95% CI 7–14) and live birth was 11 (95% CI 7–16). Hysteroscopy in asymptomatic woman prior to their first IVF cycle could improve treatment outcome when performed just before commencing the IVF cycle. Robust and high-quality randomized trials to confirm this finding are warranted.

Introduction

IVF is an expensive treatment but results in a successful outcome in only a third of treatment cycles (Bouwmans et al., 2008). Implantation failure could be due to a variety of reasons, including embryo quality and uterine receptivity, but remains unexplained in many cases (Margalioth et al., 2006).

The presence of uterine pathology may negatively affect the chance of implantation (Cenksoy et al., 2013). The prevalence of unsuspected uterine pathology in asymptomatic...
women with implantation failure has been reported to be as high as 50% (Campo et al., 2009; Cenksoy et al., 2013; Chen et al., 2012; Fatemi et al., 2010; Feghali et al., 2003; Karayalçın et al., 2010; Kasius et al., 2009; Moini et al., 2012; Mosin et al., 2010; Sugihara et al., 2010). Therefore, one of the common investigations proposed for women undergoing IVF treatment is to evaluate the uterine cavity via hysteroscopy.

Hysteroscopy is the gold standard test for assessing the uterine cavity (Pundir and El Toukhy, 2010). It is generally performed as a definitive diagnostic tool to evaluate abnormal findings on hysterosalpingogram or saline hysterosonography performed during the course of investigation of subfertile women (Ayida et al., 1997; Brown et al., 2000; Loverro et al., 2001; Narayan and Goswamy, 1993; Roma et al., 2004). Hysteroscopy not only provides accurate visual assessment of the uterine cavity, but also provides a chance to treat any pathology detected during the examination. The availability of hysteroscopes with smaller diameter has made the use of outpatient or office hysteroscopy feasible as a routine examination (De Placido et al., 2007).

Currently, there is evidence that performing hysteroscopy before starting IVF treatment could increase the chance of pregnancy in the subsequent IVF cycle in women who had one or more failed IVF cycles (Bosteeels et al., 2010; El-Toukhy et al., 2008). However, recommendations regarding the efficacy of routine use of hysteroscopy prior to starting the first IVF treatment cycle are lacking.

This study sought to systematically review and summarize existing evidence related to the impact of routine hysteroscopy prior to starting the first IVF cycle on treatment outcome in asymptomatic women to further guide clinical practice.

Materials and methods

Literature search methodology

MEDLINE, EMBASE and Cochrane Library was searched from database inception until March 2013 for the relevant studies. The search also included ISI Conference Proceedings after 1990, as well as databases for registration of ongoing and archived randomized controlled trials (RCT), namely the International Standard Randomized Controlled Trial Number (ISRCTN) register and the metaRegister for Randomized Controlled Trials. A combination of medical subject headings and text words were used to generate two subsets of citations, one including studies of IVF and intracytoplasmic sperm injection (‘in-vitro fertilization’, ‘intracytoplasmic sperm injection’, ‘IVF’ and ‘ICSI’) and the other including studies of outpatient hysteroscopy (‘hysteroscopy’). These subsets were combined using ‘AND’ to generate a set of citations relevant to the research question. The reference lists of all known primary and review articles were examined to identify cited articles not captured by electronic searches. No language restrictions were placed in any of the searches.

Study selection and outcome measures

Studies were selected if the target population were infertile women undergoing their first IVF cycle (with or without intracytoplasmic sperm injection). The study group included women who had hysteroscopy performed in the menstrual cycle preceding the IVF treatment cycle and the control group included women who started their first IVF cycle without a prior hysteroscopy in the menstrual cycle preceding the IVF treatment. Two different types of study designs were included: randomized and non-randomized controlled studies. The primary outcome measures considered were the clinical pregnancy rate (CPR) and live birth rate (LBR) achieved in the index IVF cycle. The occurrence of procedure-related complications was considered as a secondary outcome.

Studies were selected in a two-stage process. Firstly, two reviewers scrutinized the titles and abstracts from the electronic searches independently (VP and KO) and full manuscripts of all citations that was likely to meet the predefined selection criteria were obtained. Secondly, final inclusion or exclusion decisions were made on examination of the full manuscripts. In cases of duplicate publication, the most recent or complete versions were selected. Assessment of the manuscripts was performed independently by two reviewers (VP and KO), and any disagreements about inclusion were resolved by consensus after consultation with a third reviewer (TET).

Data extraction

Two reviewers (JP and VP) completed data extraction and quality assessment. The selected studies were assessed for methodological quality by using the components of study design that are related to internal validity (Centre for Reviews and Dissemination, 2001). For randomized studies, information on the method of randomization, allocation concealment, blinding, intention-to treat analysis and follow-up rates was sought by examining the full text articles. For non-randomized studies, the meta-analysis of observational studies in epidemiology (MOOSE) guidelines were followed (Stroup et al., 2000). Study characteristics such as participant features (primary or secondary infertility, other investigations for uterine cavity assessment), nature of intervention, timing of hysteroscopy and occurrence of procedure-related complications were extracted from each study. Authors of selected studies were contacted to provide missing or unclear information on trial methods or data.

Statistical analysis

From each study, binary data were extracted in 2 x 2 tables and the results were pooled and expressed as relative risks (RR) with 95% confidence intervals (CI) using fixed-effects (Mantel and Haenszel, 1959) and random-effects models as appropriate (DerSimonian and Laird, 1986). The outcome data from randomized and non-randomized evidence were initially pooled separately, and then together. Heterogeneity of the exposure effects was evaluated graphically using forest plots (Lewis and Clarke, 2001) and statistically using the I² statistic to quantify heterogeneity across studies (Higgins and Thompson, 2002).

Exploration of clinical heterogeneity was conducted using variation in features of the population, intervention and study quality. All statistical analyses were performed
using the RevMan 5 software (The Cochrane Collaboration, Oxford, UK). The level of statistical significance was set as \( P = 0.05 \). To assess for publication bias, a funnel plot analysis using the Egger test was performed (Egger et al., 1997). Subgroup analysis was also performed with participants in the hysteroscopy group divided on the basis of the hysteroscopy result.

**Results**

The process of literature identification and selection is summarized in Figure 1. Of the 217 citations identified in the search, 23 were selected upon initial screening. On examination of full manuscripts, 17 studies were excluded (Table 1) and six articles, including a total of 3179 participants, satisfied the selection criteria for this review (Table 2). One randomized and five non-randomized controlled studies were found comparing office hysteroscopy with no intervention in the cycle preceding the first IVF cycle. There is one RCT registered in metaRegister for Randomized Controlled Trials in women undergoing their first IVF cycle with normal scan findings (inSIGHT study, Smit et al., 2012).

**Quality of the included studies**

One randomized (El-Nashar and Nasr, 2011) and five observational controlled studies (Doldi et al., 2005; Kilic et al., 2013; Karayalçin et al., 2012; Trninic-Pjević et al., 2011; Yu et al., 2012) examined the impact of hysteroscopy on the outcome of the subsequent IVF cycle in patients having their first IVF attempt. The control group in those studies represented patients in whom IVF treatment was started without a prior hysteroscopy in the preceding cycle. All six studies were single-centre trials and included 1277 women who had hysteroscopy and 1902 women who did not have a hysteroscopy prior to starting IVF. The quality of the six studies and their main characteristics are presented in Tables 2–4.

The study of Doldi et al. (2005) included 600 patients: 300 patients with normal pelvic ultrasound scan and hyosalpingogram who had hysteroscopy and endometrial biopsy in the follicular phase just before starting their first IVF cycle were compared with 300 patients with similar characteristics who did not have a hysteroscopy before their first IVF cycle. There were no significant differences between the two groups with regards to ovarian stimulation characteristics, number of oocytes retrieved and number and quality of embryos transferred. The CPR was significantly higher in the hysteroscopy group (38% versus 18%, \( P = 0.02 \)). The authors reported no difference within the hysteroscopy group in the CPR between those who had a normal hysteroscopy and those who had pathology treated at hysteroscopy. No procedure-related complications were reported in the hysteroscopy group.
The study of El-Nashar and Nasr (2011) randomized 124 women with primary infertility, scheduled to start their first intracytoplasmic sperm injection (ICSI) cycle into two groups. The intervention group (n = 62) underwent hysteroscopy with directed biopsy and correction of any intrauterine abnormalities encountered and the control group (n = 62) started their ICSI cycle without undergoing a hysteroscopy. Both groups were comparable regarding baseline patient and IVF cycle characteristics. The CPR among women in hysteroscopy group was significantly higher compared with the control group (40.3% versus 24.2%; P = 0.06).

The study of Karayalcin et al. (2012) compared IVF outcome when routine hysteroscopy was performed immediately prior to starting the first IVF/ICSI cycle (n = 407)
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with that in cycles where hysteroscopy was performed more than 6 months prior to starting IVF/ICSI (i.e. remote hysteroscopy, n = 571). The authors reported no difference between the two groups with respect to age, duration of infertility, basal hormonal parameters, treatment protocol and IVF/ICSI cycle characteristics. The implantation rate (22.1% versus 11.1%, \(P < 0.05\)), CPR (45.2% versus 27.1%, \(P < 0.05\)) and LBR (36.9% versus 22.6%, \(P < 0.05\)) were significantly higher in the immediate hysteroscopy group compared with the control group.

The study of Kilic et al. (2013) included 100 patients who underwent hysteroscopy before the first IVF–embryo transfer cycle and 398 patients who did not undergo hysteroscopy before starting their first IVF–ET cycle (every fifth patient who met the study inclusion criteria underwent hysteroscopy). The two groups were similar with respect to baseline characteristics. The LBR in the hysteroscopy group was significantly higher compared with the control group (26% versus 18.3%, \(P < 0.05\)).

The study of Trninic-Pjević et al. (2011) included 480 patients who had a normal transvaginal ultrasound scan within 2 months prior to their first IVF cycle. Of these, 193 had a hysteroscopy before starting IVF treatment and 287 started IVF without prior hysteroscopy. There were no differences in the mean age, duration of infertility and number of mature oocytes retrieved in the two groups. The CPR (43.5% versus 36.9%, \(P < 0.05\)) and LBR (35.2% versus 27.5%, \(P < 0.05\)) were significantly higher in the hysteroscopy group compared with the control group.

The study of Yu et al. (2012) included 215 women who underwent hysteroscopy before starting the first IVF treatment cycle and 284 women who only had transvaginal sonography prior to starting IVF. The age, infertility duration, basal FSH concentrations, total antral follicle count, total gonadotrophin consumption, endometrial thickness, number of oocytes retrieved and fertilization rate were similar in both groups. The authors reported no significant differences in the CPR (43% versus 44%), miscarriage rate (15.2% versus 16%) and LBR (34% versus 35.6%) per cycle between the two groups. However, they reported that patients who underwent operative hysteroscopy had a significantly higher LBR for the first IVF/ICSI cycle in comparison with those who had a normal hysteroscopy (51.2% versus 33.6%, \(P = 0.02\)).

Primary outcome measures

Clinical pregnancy rate

Five of the six studies reported the CPR after IVF treatment (Doldi et al., 2005; El-Nashar and Nasr, 2011; Karayalçın et al., 2012; Trninic-Pjević et al., 2011; Yu et al., 2012). In total, 2681 participants were included in these five studies: 1177 participants in the hysteroscopy group and 1504 in the control group. Results of the RCT showed a higher CPR in the hysteroscopy group (RR 1.67, 95% CI 0.98–2.84). Results of the four non-RCT showed a significant improvement in CPR in the hysteroscopy group compared with the control group (RR 1.41, 95% CI 1.03–1.94, \(P = 0.03\)). Pooling of the results from all five studies showed a significantly higher CPR in the subsequent IVF cycle in the hysteroscopy group (RR 1.44, 95% CI 1.08–1.92, \(P = 0.01\) (Figure 2)). The number needed to treat (NNT) to achieve one additional clinical pregnancy after hysteroscopy was 10 (95% CI 7–14).

Live birth rate

Four non-randomized studies reported the LBR after IVF treatment (Karayalçın et al., 2012; Kilic et al., 2013; Trninic-Pjević et al., 2011; Yu et al., 2012). Pooled results from all

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**Table 3** Characteristics of studies comparing routine use of hysteroscopy with no hysteroscopy prior to IVF/ICSI.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Oral abstract/published data</th>
<th>No. of participants</th>
<th>Office hysteroscopy</th>
<th>No intervention</th>
<th>Outcomes reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doldi et al. (2005)</td>
<td>Published</td>
<td>600</td>
<td>300 with 5 mm OH</td>
<td>300</td>
<td>CPR, complications</td>
</tr>
<tr>
<td>Karayalçın et al. (2012)</td>
<td>Published</td>
<td>978</td>
<td>407 with 5 mm OH</td>
<td>571 with remote hysteroscopy; patients who underwent OH at a previous time &gt;6 months</td>
<td>CPR, LBR</td>
</tr>
<tr>
<td>Kilic et al. (2013)</td>
<td>Published</td>
<td>498</td>
<td>100</td>
<td>398</td>
<td>CPR, LBR, including in subgroups of diagnostic and operative OH</td>
</tr>
<tr>
<td>Trninic-Pjević et al. (2011)</td>
<td>Published</td>
<td>480</td>
<td>193</td>
<td>287</td>
<td>CPR and LBR, including in subgroups of diagnostic and operative OH</td>
</tr>
<tr>
<td>Yu et al. (2012)</td>
<td>Published</td>
<td>499</td>
<td>215</td>
<td>284</td>
<td>CPR, miscarriage rate, LBR, including in subgroups of diagnostic and operative OH</td>
</tr>
</tbody>
</table>

CPR = clinical pregnancy rate; LBR = Live birth rate; OH = office hysteroscopy.
four studies showed a significantly higher LBR in the subsequent IVF cycle in the hysteroscopy group (RR 1.30, 95% CI 1.00–1.67, \( P = 0.05 \)) (Figure 3). The NNT to achieve one additional live birth after hysteroscopy was 11 (95% CI 7–16).

**Sensitivity analysis**

A sensitivity analysis was performed to compare IVF outcome in women who had a normal hysteroscopy with those who had operative hysteroscopy to correct intrauterine pathology. Pooled data showed no significant difference in the CPR (RR 1.14, 95% CI 0.47–2.80; Figure 4) and the LBR (RR 0.86, 95% CI 0.37–2.02; Figure 5) between the two groups.

**Publication bias**

Funnel plot analysis for publication and related biases did not suggest evidence of bias (Egger test not significant; Figure 6).

**Hysteroscopy-related complications and additional procedures**

Five studies reported no procedure-related complications (Doldi et al., 2005; El-Nashar and Nasr, 2011; Karayaçın et al., 2012; Trninic-Pjević et al., 2011; Yu et al., 2012). Only one study (Kilic et al., 2013) reported on the completeness of office hysteroscopy in their population. Three out of 41 intrauterine pathologies encountered (7%) could not be

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### Table 4 Patient characteristics and hysteroscopy details in studies comparing routine use of hysteroscopy compared with no hysteroscopy prior to IVF/ICSI

<table>
<thead>
<tr>
<th>Publication</th>
<th>Type of infertility</th>
<th>Inclusion criteria</th>
<th>Exclusion</th>
<th>Previous investigations</th>
<th>Timing of hysteroscopy</th>
<th>Hysteroscopy details</th>
<th>Abnormal findings (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doldi et al. (2005)</td>
<td>Subfertility for at least 1 year; primary or secondary; 73% primary</td>
<td>All ages</td>
<td>Thyroid dysfunction; elevated prolactin</td>
<td>HSG within previous year and TVS within previous 2 months normal</td>
<td>Follicular phase, before starting stimulation for IVF cycle</td>
<td>Water—distension media; monopolar operative hysteroscope 9 mm; 3% mannitol distension media; endometrial sample taken in all by aspiration with 4 mm cannula</td>
<td>40</td>
</tr>
<tr>
<td>El-Nashar and Nasr (2011)</td>
<td>Primary subfertility</td>
<td>Infertility for 3 years; no prior term delivery</td>
<td>TVS</td>
<td>Within 50 days of IVF cycle.</td>
<td>Rigid 4 mm hysteroscope; 2% glycine as distension media</td>
<td>NA</td>
<td>9.7</td>
</tr>
<tr>
<td>Karayaçın et al. (2012)</td>
<td>Diagnosis of infertility and scheduled for IVF/ICSI</td>
<td>≤39 years; BMI ≤ 30</td>
<td>ND</td>
<td>Follicular phase (days 5–7 of menstrual cycle)</td>
<td>Local anaesthesia; sedative; 4 mm scope; normal saline distension media</td>
<td>Intrauterine pathologies treated during OH</td>
<td>41</td>
</tr>
<tr>
<td>Kilic et al. (2013)</td>
<td>Not reported</td>
<td>Age &lt; 38 years</td>
<td>ND</td>
<td>TVS within previous 2 months</td>
<td>Follicular phase</td>
<td>5 mm hysteroscope; 6.5 mm operative hysteroscope; normal saline as distension media</td>
<td>58.6</td>
</tr>
<tr>
<td>Yu et al. (2012)</td>
<td>Not reported</td>
<td>Women undergoing first IVF treatment</td>
<td>ND</td>
<td>HSG, TVS Early follicular phase</td>
<td>No anaesthesia; 3.1 mm flexible hysteroscope; dextrose 5% distension medium; intrauterine lesions treated with transcervical resection using operative hysteroscopes under general anaesthesia</td>
<td>16.7</td>
<td></td>
</tr>
</tbody>
</table>

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-- = no data available; HSG = hysterosalpingogram; NA = not applicable; OH = office hysteroscopy; TVS = transvaginal ultrasound scan.
treated with office hysteroscopy; a uterine septum extending from the level of the cervical isthmus to the uterine fundus needed a 2-stage operative hysteroscopy and two type-1 submucosal myoma of 3 and 4 cm in size needed operative hysteroscopy. One patient (1%) had severe cervical stenosis with failed initial office hysteroscopy, but had a successful

Figure 2  Clinical pregnancy rate per cycle for routine hysteroscopy versus no hysteroscopy prior to IVF/ICSI.

Figure 3  Live birth rate per cycle for routine hysteroscopy versus no hysteroscopy prior to IVF/ICSI.

Figure 4  Clinical pregnancy rate per cycle for normal hysteroscopy versus abnormal hysteroscopy (operative) prior to IVF/ICSI.

Figure 5  Live birth rate per cycle for normal hysteroscopy versus abnormal hysteroscopy (operative) prior to IVF/ICSI.
office hysteroscopy after receiving 200 μg misoprostol vaginally 2 days later. One patient (1%) had endometrial damage at hysteroscopy, but had a successful pregnancy and live birth after the IVF cycle. Ten patients had a second-look hysteroscopy after previous adhesolysis, all of which revealed no adhesion reformation.

Discussion

Evidence exists that performing hysteroscopy before IVF treatment significantly increases the chance of pregnancy in the subsequent IVF cycle in women who had one or more failed IVF cycles (Bosteels et al., 2010; Demiroğlu and Gurgan, 2004; El-Toukhy et al., 2008; Rama Raju et al., 2006). However, the place of routine hysteroscopy prior to starting the first cycle IVF cycle has not been evaluated systematically. This systematic review examined the available evidence on the role of routine hysteroscopy prior to the first IVF/ICSI in asymptomatic women with normal ultrasound scan findings. It adopted strict criteria to identify studies which met the inclusion criteria and it excluded studies which included a mixed population of patients having the first and subsequent IVF cycle (Mooney and Milki, 2003; Shawki et al., 2012).

Data presented in this systematic review and meta-analysis suggests that hysteroscopy performed in the cycle preceding the ovarian stimulation cycle could improve IVF outcome in asymptomatic patients with a normal transvaginal ultrasound scan having their first and subsequent IVF cycle (Mooney and Milki, 2003; Shawki et al., 2012).

The prevalence of unsuspected intrauterine abnormalities identified at hysteroscopy in asymptomatic IVF population has been reported to be as high as 50% (Fatemi et al., 2010; Hinckley and Milki, 2004; Karayalcin et al., 2010; Kasius et al., 2009). In the six studies included in the current review, this ranged from 10% to 59%. Uterine cavity abnormalities such as endometrial polyps, submucous myomas, intrauterine adhesions and uterine septa could have a negative impact on successful implantation (Pérez-Medina et al., 2005 Bosteels et al., 2010; De Angelis et al., 2010). Diagnosis and treatment of those abnormalities could restore normality of the uterine cavity, optimize uterine environment and thus improve IVF success rates (Feghali et al., 2003; Oliveira et al., 2003; Sugiura et al., 2010). Sensitivity analysis showed there was no significant difference in the CPR between patients who had hysteroscopic correction of uterine pathology compared with those who had normal hysteroscopy.

The current results, as well as those of others, also suggest that the benefit of hysteroscopy could extend beyond correction of uterine pathology. Easier embryo transfer, more accurate embryo placement and enhanced endometrial receptivity secondary to endometrial stimulation have been considered as plausible explanations for the improved IVF outcome after normal hysteroscopy (Dhulkotia et al., 2012; Egbase et al., 2000; El-Toukhy et al., 2012; Mansour and Aboulghar, 2002; Pabuccu et al., 2005; Potdar et al., 2012; Shohayeb and El-Khayat, 2012). Indeed, in the study of Doldi et al. (2005), patients in the hysteroscopy group had endometrial biopsy, which could have contributed to the increased pregnancy rate in the study group.

It is interesting that the degree of improvement in IVF outcome observed after hysteroscopy prior to the first IVF

![Funnel plot](image)
cycle seems to be lower than that observed after hystero-
scopy following previous IVF failure (El-Toukhy et al.,
2008), consequently resulting in a higher NNT to achieve
an additional clinical pregnancy (11 versus 7, respec-
tively). Women having their first IVF cycle are probably
different in their fertility potential compared with those
who had one or more failed IVF attempts. Therefore,
the margin of improvement in IVF outcome after hystero-
scopy could be narrower, reflecting the lower burden of
uterine pathology expected in those having their first IVF
cycle (Fatemi et al., 2010). This observation should be
considered when planning the size of future studies on
hysteroscopy before the first IVF cycle.

Although office hysteroscopy is a simple and safe min-
imally invasive procedure that could be readily incorpo-
rated into IVF programmes in most assisted reproduction
centres (El-Mazny et al., 2011; Hinckley and Milki, 2004;
Karayalcin et al., 2010; Lorusso et al., 2008; Surrey,
2012), the results of the current review should be inter-
preted with caution. There was considerable methodolog-
ical and statistical heterogeneity among the studies
included in this review. Furthermore, only one of the six
studies was randomized and was published as a conference
abstract. Evidence from larger randomized trials on the
feasibility and efficacy of office hysteroscopy prior to
the first IVF cycle is required to confirm this study’s
findings.

In conclusion, this systematic review and meta-analysis
of published controlled studies suggests that hysteroscopy
in asymptomatic women prior to their first IVF cycle could
be associated with improved treatment outcome when per-
formed just before commencing the IVF cycle. Robust and
high-quality randomized trials to confirm this finding are
needed to further guide clinical practice.

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