Hysteroscopy before in-vitro fertilisation (inSIGHT): a multicentre, randomised controlled trial


Summary

Background Hysteroscopy is often done in infertile women starting in-vitro fertilisation (IVF) to improve their chance of having a baby. However, no data are available from randomised controlled trials to support this practice. We aimed to assess whether routine hysteroscopy before the first IVF treatment cycle increases the rate of livebirths.

Methods We did a pragmatic, multicentre, randomised controlled trial in seven university hospitals and 15 large general hospitals in the Netherlands. Women with a normal transvaginal ultrasound of the uterine cavity and no previous hysteroscopy who were scheduled for their first IVF treatment were randomly assigned (1:1) to either hysteroscopy with treatment of detected intracavitary abnormalities before starting IVF (hysteroscopy group) or immediate start of the IVF treatment (immediate IVF group). Randomisation was done with web-based concealed allocation and was stratified by centre with variable block sizes. Participants, doctors, and outcome assessors were not masked to the assigned group. The primary outcome was ongoing pregnancy (detection of a fetal heartbeat at >12 weeks of gestation) within 18 months of randomisation and resulting in livebirth. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01242852.

Findings Between May 25, 2011, and Aug 27, 2013, we randomly assigned 750 women to receive either hysteroscopy (n=373) or immediate IVF (n=377). 209 (57%) of 369 women eligible for assessment in the hysteroscopy group and 200 (54%) of 373 in the immediate IVF group had a livebirth from a pregnancy during the trial period (relative risk 1.06, 95% CI 0.93–1.20; p=0.41). One (<1%) woman in the hysteroscopy group developed endometritis after hysteroscopy.

Interpretation Routine hysteroscopy does not improve livebirth rates in infertile women with a normal transvaginal ultrasound of the uterine cavity scheduled for a first IVF treatment. Women with a normal transvaginal ultrasound should not be offered routine hysteroscopy.

Funding: The Dutch Organisation for Health Research and Development (ZonMW).

Introduction In-vitro fertilisation (IVF) is considered to be one of the major medical breakthroughs of the 20th century. The use of IVF has increased gradually since the birth of Louise Brown in 1978, and more than 5 million children are estimated to have been born with the help of this technology. However, only 25–30% of cycles of IVF and intracytoplasmic sperm injection (ICSI) lead to the birth of a child. Although both ovum collection and fertilisation are usually successful, a largely unexplained gap remains between the number of embryo transfers and the number of ongoing pregnancies (defined as >12 weeks of gestation). The cause of this implantation failure is poorly understood but is thought to be determined by both the embryo and the uterine cavity. Studies suggest the most frequent cause is chromosomal abnormalities in the embryo, but abnormalities of the uterine cavity such as polyps, myoma, and adhesions are also thought to be associated with impaired implantation and reduced chance of pregnancy. Hysteroscopy is regarded as the reference standard to detect these uterine abnormalities. Hysteroscopy is thought to improve pregnancy rates in women scheduled for IVF through detection and surgical removal of uterine cavity abnormalities; dilatation of the cervical canal to allow future embryo transfer; or induction of an inflammatory reaction of the endometrium by the procedure itself. Investigators of two randomised controlled trials reported increased pregnancy rates of up to 13% after hysteroscopy in women with two or more failed IVF treatment cycles. In clinical practice, hysteroscopy is often done routinely in infertile women scheduled for their first IVF cycle. The likelihood of detecting a difference in livebirth rates might be lower in women undergoing screening hysteroscopy before a first cycle of IVF or ICSI than in women with repeated IVF failure; however, if hysteroscopy, detection, and treatment of unexpected abnormalities seems to be effective in a third cycle, it would not make sense to first do two cycles of IVF and then hysteroscopy in women who have undetected uterine cavity abnormalities. Two recent studies on the effectiveness of routine hysteroscopy in women scheduled for first IVF are of poor quality. We planned the inSIGHT trial, a multicentre randomised
Research in context

Evidence before this study

We searched PubMed and the Cochrane Library for meta-analyses and randomised controlled trials investigating the effectiveness of hysteroscopy in women scheduled for first in-vitro fertilisation (IVF) published up to Dec 22, 2015. We used combinations of the following keywords “IVF”, “ICSI”, “assisted reproductive technology”, “fertility therapy”, “infertility”, “reproductive medicine”, “hysteroscopy”, and “reproductive surgery”. We identified one meta-analysis and one additional randomised controlled trial. The 2014 meta-analysis selected all published and unpublished studies investigating the effectiveness of hysteroscopy before first IVF or intracytoplasmic sperm injection (ICSI) treatment cycle. On the basis of four cohort studies and one unpublished randomised trial the authors concluded that the livebirth rate was increased after hysteroscopy. The unpublished randomised controlled trial reported only the clinical pregnancy rate, which was nearly twice as high in the 62 women who had a hysteroscopy compared with the 62 women who immediately started ICSI. Considering the poor quality of the trial and the inclusion of non-randomised studies, which have a high risk of bias, the results of this meta-analysis should be interpreted with caution. One recent randomised controlled trial, which was not included in the meta-analysis, showed improved pregnancy rates of up to 70% after hysteroscopy in women scheduled for a first ICSI treatment. However, this study had major methodological flaws, including no power calculation, no description of the definition of pregnancy rate, no recording of ongoing pregnancy or livebirth rate, and no report of the number of participants undergoing a second therapeutic hysteroscopy. Both the meta-analysis and the randomised controlled trial were not yet published when the inSIGHT study was designed and initiated.

Added value of this study

The inSIGHT study is a large robust randomised controlled trial investigating livebirth rates after hysteroscopy in women with a normal transvaginal ultrasound scheduled for a first IVF or ICSI treatment cycle. Our study showed no increase in livebirth rates after hysteroscopy. A recent randomised controlled trial (TROPHY study) investigating the effectiveness of hysteroscopy in women with two to four failed IVF treatment cycles also reported no effect of hysteroscopy on livebirth rates.

Implications for all the available evidence

Hysteroscopy should not be done in women with a normal transvaginal ultrasound undergoing IVF or ICSI treatment because it does not improve IVF outcomes.

Methods

Study design and participants

The inSIGHT trial was a pragmatic multicentre, randomised controlled trial done within the Dutch Consortium for Research in Women’s health and in seven university hospitals and 15 large general hospitals in the Netherlands. Recruitment of eligible women and counselling was done by staff or research nurses of participating hospitals. The study protocol was published previously. Women were eligible for the trial if they were infertile, scheduled to start IVF or ICSI treatment, and had a normal transvaginal ultrasound of the uterine cavity (defined as no visible intracavity pathology—e.g., submucous myomas, polyps, or septa). Transvaginal ultrasound (2D) was done as part of the fertility work-up by gynaecologists, trained physicians, or specialised nurses. We excluded women with a history of two or more miscarriages or intermenstrual blood loss and those who had undergone hysteroscopy previously. All women gave written informed consent. Ethics approval for the study was obtained from the institutional review board of the University Medical Center Utrecht (MEC 10-272). The board of directors of all participating centres approved the study.

Randomisation and masking

We randomly assigned women to hysteroscopy followed by IVF (hysteroscopy group) or to immediate IVF (immediate IVF group) in a 1 to 1 ratio. Research nurses or the local investigator of the participating hospitals used web-based randomisation with a variable block size to allocate patients to groups and stratified assignment by centre. Because of the nature of the intervention, we did not mask the participants, doctors, or outcome assessors to the assigned group.

Procedures

Women assigned to the intervention group were scheduled for hysteroscopy in the early to midfollicular phase of the menstrual cycle in an outpatient setting without anaesthesia, 1–3 months before the start of IVF treatment. A paracervical block was offered in cases of patient intolerance. The surgeon inspected the endocervical canal, the endometrial lining of the uterine cavity, and tubal orifices and recorded all findings on a standardised form. Intrauterine abnormalities were defined as the presence of polyps, myoma, adhesions, or uterine malformations. All participating centres received instructions for the hysteroscopy procedure, including images of intrauterine abnormalities before the start of the study. Therapeutic hysteroscopy was done in the same session if intrauterine abnormalities were detected, or postponed to a setting with anaesthesia if necessary. The need for septum resection in a subsequent session
was at the judgment of the gynaecologists. Hysteroscopies were done by a maximum of two gynaecologists per centre. In five hospitals (UMC Utrecht, Maxima Medical Center, Academic Medical Center Amsterdam, Isala clinics, and Maastricht University Medical Center) saline infusion sonography was done prior to hysteroscopy as part of a substudy, which will be reported separately. All randomised women were scheduled for IVF as described in the study protocol. In cases of poor response after IVF stimulation, escape intrauterine insemination could be done according to the local protocol of the participating centres. No other treatment strategies were provided as part of the study after multiple failed IVF cycles, other than repeating the IVF or ICSI procedure, because insufficient evidence is available for interventions for implantation failure. Pregnancy tests (urine or serum human chorionic gonadotropin) were done 14 days after embryo transfer. Women with a positive pregnancy test were scheduled for transvaginal ultrasound at 7 weeks and between 10 weeks and 12 weeks of gestation if the first ultrasound showed an intrauterine pregnancy. The outcome of the pregnancy was obtained through a questionnaire or telephone contact by research nurses. Women were contacted through a questionnaire or telephone contact if the pregnancy outcome was not available from the clinical file. If they did not reply after multiple telephone contact, then follow-up was considered to be incomplete.

We collected data for a cost-effective analysis through the health and labour questionnaire. Visual analogue scale score was recorded after both saline infusion sonography and hysteroscopy and was collected as part of the substudy that will be reported separately. Adverse events were reported to the principal investigator by the staff and research nurses of participating hospitals and administrated centrally.

**Outcomes**
The primary outcome was ongoing pregnancy within 18 months of randomisation and resulting in livebirth (defined as delivery of a live fetus after 24 weeks of gestation). Prespecified secondary outcomes were cumulative rates of implantation (defined as a positive pregnancy test after embryo transfer) and miscarriage (defined as absence of a fetal heartbeat at week 7 or week 12 of gestation) and the prevalence of intrauterine abnormalities. We also aimed to assess cost calculations and patient preference and tolerance of the procedures.

**Statistical analysis**
To calculate the sample size needed we assumed that, compared with immediate IVF, hysteroscopy would increase the chance of a livebirth from 30% to 40%. To detect this difference, we needed to include 350 women per group (700 women overall) to provide 80% power at α 5%. Anticipating that 5% of the women in the intervention group would not undergo hysteroscopy, we established that the final sample size needed to be 370 women per study group (740 women overall).

Analyses for the primary and secondary outcomes were done by intention to treat. Women with incomplete follow-up were considered not pregnant at 18 months of follow-up. To calculate p values we used χ² tests for categorical variables and independent samples t tests for continuous variables. Differences in outcomes between the groups were expressed as relative risks (RR) with 95% CI. For the primary outcome we calculated a risk difference, which was calculated by subtracting the cumulative livebirth rate in the hysteroscopy group from the cumulative incidence in the immediate IVF group. Kaplan-Meier curves were constructed to express time to ongoing pregnancy (defined as the detection of a fetal heartbeat on ultrasound at >12 weeks of gestation) resulting in livebirth. The log-rank test was used to test for significance in the Kaplan Meier Curve. We also calculated a hazard ratio and a 95% CI. In the analysis of pregnancies per embryo transfer, clustering of multiple embryo transfers per woman had to be taken into account: risk ratios were obtained from a generalised estimating equation model with binomial response and a log link, assuming independent working correlation.
Baseline characteristics

Table 1: Data are n (%) or mean (SD). IVF = in-vitro fertilisation. *From active child wish (or last miscarriage) until the first stimulation day in the first treatment cycle. †Including patients with more than one cause of subfertility. ‡Defined as referred from general practitioner. Smoking was more common in the immediate IVF group compared with 26 (7%) women in the hysteroscopy group (RR 1.23, 95% CI 1.02–1.42; p = 0.043; table 3).

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 25, 2011, and Aug 27, 2013, we enrolled 750 women, assigning 373 to the hysteroscopy group and 377 to the immediate IVF group (figure 1). The last participant was followed-up in February, 2014. Baseline characteristics for the groups were similar, except smoking was more common in the immediate IVF group (table 1).

325 (88%) women in the hysteroscopy group underwent hysteroscopy (figure 1; appendix). Median time between randomisation and hysteroscopy in this group was 20–6 days (IQR 10.6–33.6). The hysteroscopy procedure was not completed in 29 (9%) women due to pain or a difficult passage of the internal os; two of these procedures to one or more centres was present (p = 0.15). Data for patient preference, tolerance, and outcomes with saline infusion sonography will be reported elsewhere.

The hysteroscopy findings and IVF treatment characteristics are summarised in the appendix. We detected 43 abnormalities in 37 women, of which 31 abnormalities were treated (appendix). Septum resection was done in one woman. After discussion, septum resection was not done in five other women, which was according to the study protocol. One polyp located in the tubal orifice was not treated because it was too painful for the participant and she refused general anaesthesia thereafter. Two women with myoma (one with grade I, one with grade II) did not have treatment due to technical difficulties.

For the primary outcome, 209 (57%) women allocated to hysteroscopy had ongoing pregnancy resulting in livebirth, compared with 200 (54%) allocated to immediate IVF (RR 1.06, 95% CI 0.93–1.20; p = 0.41; table 2). The risk difference was 3% (95% CI –4% to 10%). At 18 months of follow-up, more than half of women in both groups had an ongoing pregnancy (RR 1.05, 95% CI 0.92–1.19; p = 0.45; table 2). Cumulative implantation and miscarriage rate for the 18 months follow-up could not be calculated due to spontaneous conceptions, but rates per embryo transfer did not differ between groups (table 3). Pregnancy loss per embryo transfer was greater in the hysteroscopy group than in the IVF group (RR 1.43, 95% CI 1.06–1.93; p = 0.018). Biochemical pregnancy loss was also higher in the hysteroscopy group (1.69, 1.02–2.82; p = 0.043; table 3). Pregnancy loss after first IVF cycle occurred in 26 (7%) women in the hysteroscopy group compared with 21 (6%) in the immediate IVF group (RR 1.23, 0.74–2.02; p = 0.43).

Median time from randomisation to pregnancy leading to livebirth was 161 days (IQR 87–332) in the hysteroscopy group versus 141 days (83–286) in the immediate IVF group (p = 0.52; table 2). In post-hoc analyses, the groups did not differ in rates of ongoing pregnancy, clinical pregnancy (defined as a presence of a gestational sac at 7 weeks), and multiple pregnancy (defined as at least two fetuses with a heartbeat at 12 weeks). Time to ongoing pregnancy did not significantly differ between the groups (figure 2). Because of the absence of effect of hysteroscopy, the planned cost analysis was futile and data for cost-effectiveness will not be reported.

In the hysteroscopy group, five women had an ectopic pregnancy, one fetus was found to have a chromosomal abnormality, and one woman had clinical endometritis.
In the immediate IVF group, two women had an ectopic pregnancy.

In a post-hoc analysis we re-examined the primary outcome in the per-protocol population—ie, in all women assigned to the hysteroscopy group who completed hysteroscopy before starting IVF and those assigned to the IVF group who started IVF without previous hysteroscopy. We excluded women who conceived spontaneously in the waiting period for the assigned intervention (hysteroscopy or immediate IVF) and women who received hysteroscopy during the 18 months of follow-up. 177 (54%) of 325 women who received hysteroscopy before the start of IVF had an ongoing pregnancy resulting in livebirth compared with 184 (52%) of 352 of the women who started IVF without previous hysteroscopy (RR 1.04, 95% CI 0.91–1.20; p=0.57). Of women who successfully completed hysteroscopy in the hysteroscopy group, 16 (64%) of 25 women with treated abnormalities, seven (58%) of 12 with untreated abnormalities, and 143 (55%) of 259 women with a normal hysteroscopy had an ongoing pregnancy resulting in a livebirth. The livebirth rate did not differ between women with and without treated abnormalities (p=0.69). We assessed whether treatment of abnormalities would change the primary outcome. Had the eight women with untreated abnormalities all had a livebirth, the groups would still not differ significantly for rate of ongoing pregnancy resulting in a livebirth (RR 1.08, 95% CI 0.95–1.20; p=0.22).

Discussion

Findings from this randomised controlled trial show that hysteroscopy does not improve livebirth rates in women with a normal transvaginal ultrasound of the uterine cavity who are scheduled for their first IVF cycle. Cumulative rates of pregnancy leading to a livebirth and the time to this pregnancy also did not differ between groups.
By contrast with the findings of our study, a 2014 meta-analysis from Pundir and colleagues showed increased livebirth rates after hysteroscopy in women scheduled for a first IVF cycle (RR 1.30, 95% CI 1.00–1.67; p=0.05). The findings of this meta-analysis should be questioned because the authors included one small non-published randomised trial and four non-randomised studies. Also, data for livebirth rates were incomplete.

One 2015 randomised controlled trial in women scheduled for a first IVF treatment cycle, which was not included in the meta-analysis by Pundir and colleagues, showed improved pregnancy rates of up to 70% after hysteroscopy in women scheduled for a first ICSI treatment, but this trial had methodological weaknesses.

A randomised controlled trial (TROPHY trial) investigating the role of hysteroscopy in women with two to four failed IVF cycles has reported that hysteroscopy did not improve livebirth rates, which is consistent with our reported findings.

In our trial, baseline characteristics were balanced between groups, except that more women in the immediate IVF group smoked (table 1). This discrepancy seems not to have affected the study outcome because no differences in IVF treatment characteristics were present (appendix). Also, a negative effect of smoking on pregnancy rates would have only led to further equalisation of the pregnancy outcomes between both groups.

Biochemical pregnancy loss occurred more frequently in the hysteroscopy group than in the immediate IVF group (table 3). It could be speculated that hysteroscopy might slightly improve conditions for implantation, allowing less vital embryos to implant and resulting in a biochemical pregnancy with rapid loss in the weeks thereafter. However, this pro-implantation effect of hysteroscopy would be expected to be strongest in the first cycle after hysteroscopy and no difference in pregnancy loss was found in the first IVF and ICSI treatment cycle. Therefore, the overall increased pregnancy loss in the hysteroscopy group might be a chance finding without biological significance.

Hysteroscopy has been postulated to improve IVF outcome through detection and treatment of intrauterine abnormalities, although high-quality studies are lacking. Only one randomised controlled trial has been done to investigate the effect of polyp resection in women undergoing intrauterine insemination cycles who had suspected pathology on ultrasound. This study showed improved clinical pregnancy rates after polyp resection (RR 2.1, 95% CI 1.5–2.9). In the present study, intrauterine abnormalities were detected at hysteroscopy in 12% of women without abnormalities at transvaginal ultrasound. The intrauterine abnormalities detected at hysteroscopy seemed small and, therefore, could well have remained undetected at transvaginal ultrasound. The observed detection rate of transvaginal ultrasound is in agreement with other studies. The reported sensitivity and specificity of transvaginal ultrasound compared with hysteroscopy varies between 0.75 and 0.93 and 0.60 and 0.97, respectively. Diagnostic accuracy of newer techniques such as saline-infusion sonohysterography and 3D ultrasonography could possibly be more comparable to the accuracy of hysteroscopy. By contrast with saline-infusion sonohysterography, many clinics have no experience with 3D ultrasonography. The assessment of the accuracy of saline-infusion sonohysterography in women with a normal transvaginal ultrasound before IVF will be reported separately. In the present study in which women were screened by hysteroscopy, livebirth rates were not significantly higher in women with detected and treated pathology. Although the number of women with intrauterine abnormalities was small, this finding suggests that it is neither useful nor cost-effective to use hysteroscopy to screen for intrauterine pathology in women with a normal ultrasound.

Our sample size calculation was based on a 10% difference in livebirth rates after the first treatment cycle because the positive effect of hysteroscopy was expected to be strongest in the first months after the intervention. As such, the sample size would be considered sufficient to observe a clinically relevant effect. The actual livebirth rates after 18 months of treatment were recorded because a cost-effectiveness analysis of the longer-term effects was included in the study design, and is the basis for the ZonMW funding programme. Because no clinically important difference was noted for long-term effects, a cost-effectiveness analysis was futile.

There were several important strengths and limitations to our trial. The multicentre design allows...
generalisation of our findings to both academic and non-academic hospitals. Moreover, this is the first study to investigate hysteroscopy before the start of IVF with a follow-up period of 18 months, ensuring that the possible beneficial effects of hysteroscopy on livebirth rates after several exposures to replaced embryos can be observed. The fact that hysteroscopy was done by different gynaecologists in many centres might be regarded as a limitation because studies on the diagnostic accuracy of hysteroscopy have shown that it is associated with a considerable degree of inter-observer variability.23 To minimise this operator variation in diagnosing abnormalities, we offered all participating centres instructions for the hysteroscopy procedure (including images of intrauterine pathology) before the study started. With the remaining inherent variability, the study represents daily practice variation, and as such provides answers based on real daily-life conditions. Another limitation is that 44 women did not receive the assigned hysteroscopy, which could lead to uncertainty about the true absence of an effect of hysteroscopy on livebirth rates. However, the per-protocol analysis showed similar results to the intention-to-treat analysis. A criticism of our study could be that eight women with treatable abnormalities were not operated on. However, it is unlikely that this affected the study results because three of these women had a livebirth and the primary outcome would still not differ significantly between groups had the five untreated women become pregnant. It should be mentioned that septum resection is not standard treatment in the Netherlands because the effectiveness of septum resection in improving fertility is still unclear; a trial is underway to assess this (TRUST trial; NTR1676).

In health-care systems in which hysteroscopy has become routine care, the cost reduction by stopping this practice could be considerable. For the Netherlands, total structural cost reduction is estimated to be €1·2 million a year. However, the costs of hysteroscopy and thus cost reduction might vary between countries and type of clinic. Refraining from hysteroscopy will also prevent unnecessary patient discomfort. Transvaginal ultrasound remains the basic screening method for the presence of intrauterine abnormalities and will mostly detect larger abnormalities that could prompt the need for hysteroscopy for final diagnosis and treatment. Still, the effectiveness of treating larger intracavitary abnormalities remains to be proven.26

In conclusion, the results of this large randomised controlled trial show that routine hysteroscopy before the first IVF or ICSI treatment cycle does not improve fertility prospects in infertile women with a normal transvaginal ultrasound of the uterine cavity who have not had a previous hysteroscopy. Therefore, routine hysteroscopy should not be offered to asymptomatic women scheduled for IVF.

Contributors
JCK, MJCE, HLT, FJMB, and B-WJM designed the trial. JGS, HLT, FJMB, and B-WJM coordinated the trial. JGS, CAMK, RvG, AWN, GJS, PAPM, AH, BCS, AMvH, WKHK, DAMP, KE, EMK, AS, JF, RHMD, MvH, LAL, JK, ChdK, ICAHJ, and FJMB collected the data. JGS drafted the manuscript. JGS, MJCE, HLT, FJMB, and B-WJM interpreted the data. All authors revised the report, and approved the final submitted version. HLT assumes responsibility for the completeness and accuracy of the data and analyses and for adherence to the study protocol.

Declaration of interests
We declare no competing interests.

Acknowledgments
We thank the women who participated in this study, the staff of the participating hospitals, and the office members of the Dutch Consortium for their contribution.

References


