

The effectiveness of hysteroscopy in improving pregnancy rates in subfertile women without other gynaecological symptoms: a systematic review

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BACKGROUND: Although hysteroscopy is frequently used in the management of subfertile women, a systematic review of the evidence on this subject is lacking.

METHODS: We summarized and appraised the evidence for the benefit yielded by this procedure. Our systematic search was limited to randomized and controlled studies. The QUOROM and MOOSE guidelines were followed. Language restrictions were not applied.

RESULTS: We identified 30 relevant publications. Hysteroscopic removal of endometrial polyps with a mean diameter of 16 mm detected by ultrasound doubles the pregnancy rate when compared with diagnostic hysteroscopy and polyp biopsy in patients undergoing intrauterine insemination, starting 3 months after the surgical intervention [relative risk (RR) = 2.3; 95% confidence interval (CI): 1.6–3.2]. In patients with one fibroid structure smaller than 4 cm, there was a marginally significant benefit from myomectomy when compared with expectant management (RR = 1.9; 95% CI: 1.0–3.7). Hysteroscopic metroplasty for septate uterus resulted in fewer pregnancies in patients with subfertility when compared with those with recurrent pregnancy loss (RR = 0.7; 95% CI: 0.5–0.9). Randomized controlled studies on

hysteroscopic treatment of intrauterine adhesions are lacking. Hysteroscopy in the cycle preceding a subsequent IVF attempt nearly doubles the pregnancy rate in patients with at least two failed IVF attempts compared with starting IVF immediately (RR = 1.7; 95% CI: 1.5–2.0).

CONCLUSIONS: Scarce evidence on the effectiveness of hysteroscopic surgery in subfertile women with polyps, fibroids, septate uterus or intrauterine adhesions indicates a potential benefit. More randomized controlled trials are needed before widespread use of hysteroscopic surgery in the general subfertile population can be justified.

Key words: hysteroscopy / subfertility / RCT / IVF / intrauterine insemination

Introduction

The position of hysteroscopy in current fertility practice is under debate (Shushan and Rojansky, 1999). Although there are many randomized controlled trials (RCT) on technical feasibility and patient compliance demonstrating that the procedure is well tolerated (Kremer et al., 2000; Soriano et al., 2000; Unfried et al., 2001; De Angelis et al., 2003; Guida et al., 2003; Litta et al., 2003; Pellicano et al., 2003; Marsh et al., 2004; Shankar et al., 2004; Campo et al., 2005; Sharma et al., 2005; Garbin et al., 2006; Guida et al., 2006; Sagiv et al., 2006; De Placido et al., 2007; Kabli and Tulandi, 2008;), there is no consensus on the effectiveness of hysteroscopy in improving the prognosis of subfertile women.

The Royal College of Obstetricians and Gynaecologists (RCOG) does not recommend hysteroscopy as an initial investigation unless clinically indicated, and has stated hysteroscopic treatment as a grade B recommendation in its evidence-based guidelines on fertility assessment and treatment (RCOG, 2004). It is argued that the effectiveness of operative or diagnostic hysteroscopy in the general subfertile population has not yet been proven. The European Society for Human Reproduction and Embryology has adopted a similar viewpoint (Crosignani and Rubin, 2000).

This systematic review (SR) aims to examine the effectiveness of the hysteroscopic removal of endometrial polyps, submucous fibroids, septate uterus or intrauterine adhesions in subfertile women without other gynaecological symptoms. We also aimed to study the effectiveness of diagnostic or operative hysteroscopy in women treated by IVF/intrauterine insemination (IUI). The main outcome measure studied is conception/pregnancy rate (not uncomplicated course of pregnancy).

Methods

Literature search methodology

We aimed to identify RCTs and controlled studies on hysteroscopic treatment of endometrial polyps, submucous fibroids, septate uterus or intrauterine adhesions in subfertile women without other gynaecological symptoms. Our systematic literature search included RCTs or controlled studies on the effectiveness of diagnostic or operative hysteroscopy in women undergoing IVF or IUI.

A systematic literature search using MeSH terms for 'hysteroscopy, polyps, fibroids, congenital anomalies, Asherman's syndrome, adhesions and assisted reproductive techniques' was performed in MEDLINE (1966 to November 2008), EMBASE (1974 to November 2008), CINAHL (1981 to November 2008), the Cochrane Library (1970 to November 2008) and DARE for relevant studies. This was performed independently by two researchers at

the Biomedical Libraries of the University Hospitals of Leuven and Gent, Belgium under supervision of two authors (C.M. and S.W.). The ISI Web of Knowledge version 4.4 and Scopus were also consulted. Two databases for the registration of current and archived RCTs and other controlled trials (International Standard Randomized Controlled Trial Number Register and Meta-register) were searched for relevant clinical trials.

Search filters were used for the detection of RCTs and SRs with reported sensitivities of 95 and 99% (Shojania and Bero, 2001; Robinson and Dickersin, 2002; Glanville et al., 2006). In the EMBASE and CINAHL search 'randomized controlled trial' was used instead of the MEDLINE search filters.

The detected studies were classified in two main categories.

The first group involved studies on operative hysteroscopy and pregnancy rates in subfertile patients with polyps, fibroids, septate uterus and intrauterine adhesions, with no other gynaecological symptoms. The second group included studies on diagnostic or operative hysteroscopy and pregnancy rates in subfertile patients treated by IVF or IUI.

The reference lists of all known primary articles were examined independently by four authors (J.B., B.V.H., P.P. and C.P.). There was no systematic attempt to search the grey literature.

Full manuscripts of all citations that possibly matched the predefined selection criteria were examined by four authors independently (J.B., P.P., B.V.H. and C.P.). Final inclusion or exclusion decisions were made on examination of the full manuscripts. Disagreement about inclusion was resolved by consensus after consultation with an independent fifth author (S.W.).

Study selection

RCTs or controlled studies were selected if they dealt with diagnostic or operative hysteroscopy as the study intervention and with conception defined by pregnancy rate as the main outcome measure. The study population included subfertile women without other gynaecological symptoms with polyps, fibroids, septate uterus and intrauterine adhesions or women treated by IVF or IUI.

We only included studies with conception as primary outcome measure because we aimed to measure the effectiveness of the study intervention in restoring reproductive potential. We excluded pregnancy complications such as recurrent miscarriage, premature labour or increased Caesarean section rates due to abnormal fetal presentation, although they may significantly affect a physician's decision in everyday clinical practice. Trials on diagnostic accuracy, patient compliance and cost-effectiveness were also not included.

Language restrictions were not applied.

Data extraction

The selected studies were assessed for methodological quality by using standard forms, adapted from checklists available at the Dutch Cochrane Centre website. The QUOROM guidelines were followed for RCTs and the MOOSE guidelines for non-randomized studies (Moher et al., 1999; Stroup et al., 2000). The method of randomization, allocation concealment, blinding, intention-to-treat analysis and loss to follow-up were

sought by four authors independently after detailed examination of the full text manuscripts (J.B., P.P., B.V.H. and C.P.). The authors of all selected studies were contacted to obtain missing data or give additional explanation in case of unclear study methodology.

Statistical analysis

Owing to the limited number of RCTs, additional meta-analysis or assessment for publication bias was not carried out. Original statistical analysis was performed on the data of the RCTs on polyps, fibroids and septate uterus using the software provided by the Cochrane Collaboration (Rev Man 5 version 5.0., 17 December 2008). Dichotomous data were extracted in 2×2 tables. Results were expressed as relative risks (RR) with 95% confidence intervals (CI) using fixed effects models (Mantel-Haenszel). Statistical heterogeneity was assessed with the chi-square test. Variations observed in the population characteristics, intervention and study quality were used to assess clinical heterogeneity. Statistical methodology was checked by an independent statistician at the Katholieke Universiteit Leuven, Belgium.

Results

The process of literature identification and selection is shown in Fig. 1. From the electronic search and from the examination of reference list and lists of related articles, 819 citations were found. After screening the titles and/or abstracts, 178 articles were retrieved. Finally, after investigation of the full manuscript, 30 articles were included in the SR.

We included three RCTs on the effectiveness of operative hysteroscopy in subfertile women with endometrial polyps, fibroids or septate uterus. A summary of the study characteristics of these three RCTs is presented in Table I. Moreover, we found one SR on fibroids including 22 non-randomized controlled studies.

We included two RCTs on the effectiveness of diagnostic or operative hysteroscopy in women undergoing IVF. A summary of their study characteristics is presented in Table II. We intended to do a meta-analysis of the results of these two trials, but we found a recently published meta-analysis combining the data of these two RCTs with data of three non-randomized controlled studies (El-Toukhy *et al.*, 2008).

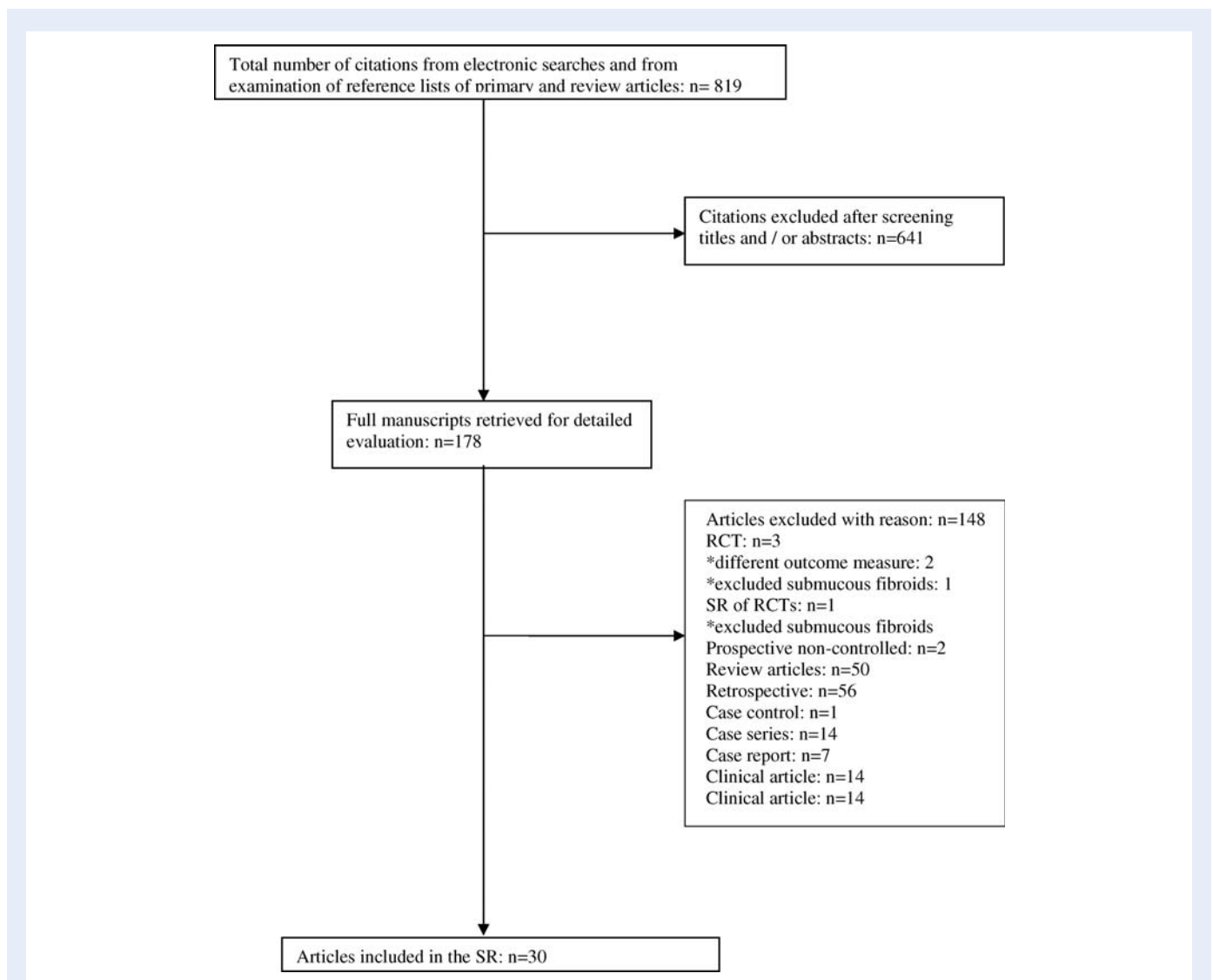


Figure 1 Flowchart for systematic review (SR) of benefit of hysteroscopy in current fertility practice.

Table I Effectiveness of operative hysteroscopy for polyps, fibroids and septate uterus on outcome (pregnancy); study characteristics

Pathology	Polyps	Fibroids	Septate uterus
Reference	Pérez-Medina et al., 2005	Casini et al., 2006	Colacurci et al., 2007
Randomization method	Computer-generated list	Randomization table	Computer-generated list
Allocation concealment	Yes	No	No
Blinding	No	No	No
Groups comparable	Unclear	Yes	Yes
Intention-to-treat analysis	No	Yes	No
Follow-up rate analysis	>95%	>95%	<85%
Power calculation	Yes	No	No
Number of included patients	215	94	160
Intervention group	Hysteroscopic polypectomy (n = 107)	Hysteroscopy and/or laparotomy (n = 52)	5 mm hysteroscopy with Versapoint (n = 80)
Control group	Diagnostic hysteroscopy (n = 108)	No surgery (n = 42)	8 mm resectoscopy (n = 80)
Outcome measure	Total pregnancy rates and time for success after four cycles	Clinical pregnancy rate after 12 months	Clinical pregnancy rate

We excluded one SR and three RCTs. Conception rate was not studied as the main outcome measure in two trials (Vercellini et al., 1993; Muzii et al., 2007). One Cochrane review (Griffiths et al., 2006) including only one underpowered randomized trial on fibroids (Seracchioli et al., 2000) excluded submucous myomas from the analysis and was therefore not included.

Does operative hysteroscopy increase the pregnancy rate in subfertile patients with a specified intrauterine pathology?

Hysteroscopic polypectomy

We found two RCTs on the hysteroscopic removal of endometrial polyps (Pérez-Medina et al., 2005; Muzii et al., 2007), of which only one trial studied the reproductive outcome after hysteroscopic polypectomy in subfertile patients with endometrial polyps undergoing IUI (Pérez-Medina et al., 2005). The main characteristics of this study are shown in Table I. The study population consisted of subfertile women with a sonographic diagnosis of endometrial polyps trying to conceive for at least 24 months and planned for IUI. An endometrial polyp was suspected when a hyperechogenic image with regular contour was demonstrated on transvaginal ultrasound (TVUS) with the presence of a vascular stalk on colour Doppler map. The polyps were detected in 452 of 2800 consecutive patients scheduled for IUI, attending the infertility clinic of a university hospital during a 50 month period. Of these 452 women, 215 patients gave informed consent for randomization. Randomization was done by a computer-generated list using an opaque-sealed envelope. Patients allocated to the intervention group (n = 107) were treated by polypectomy with a 5.5 mm continuous flow office hysteroscope, whereas in the control group (n = 108) women underwent a diagnostic hysteroscopy with polyp biopsy. Patients in the intervention and control groups were subsequently treated with four cycles of IUI with hyperstimulation with recombinant FSH starting 3 months after hysteroscopy.

Clinical pregnancy was defined as a rising level of hCG combined with TVUS visualization of a gestational sac. The clinical pregnancy rate after four IUI cycles was 63% in the polypectomy group compared with 28% in the control group (RR = 2.3; 95% CI: 1.6–3.2) (Fig. 2a) corresponding with a number needed to treat (NNT) to achieve one additional pregnancy of 3 (NNT = 3, 95% CI: 2–5). Interestingly, 65% of all pregnancies in the polypectomy group occurred before the first IUI cycle was started, resulting in a spontaneous pregnancy rate of 29% in the polypectomy group versus 3% in the control group (RR = 10; 95% CI: 3–30). Data on live birth rates were not available from this trial.

The effect of the size of the polyp was studied as a secondary outcome. The mean polyp diameter was 16 mm, with a range of 3–24 mm. Within the intervention group, a subdivision was made into four groups based on the quartiles (<5, 5–10, 11–20 and >20 mm). After hysteroscopic removal, 19 pregnancies out of 25 patients (76%) were found in the <5 mm group, 18 of 32 (56%) in the 5–10 mm group, 16 of 26 (61%) in the 11–20 mm group and 11 of 18 (61%) in the >20 mm group. No significant differences were found between the groups according to the size of the polyps ($P > 0.05$). There were no data on the number or the location of the polyps. The corresponding author confirmed that this potential secondary outcome had not been considered.

The second RCT only compared resectoscopic versus bipolar electrode excision of endometrial polyps without studying reproductive outcome (Muzii et al., 2007).

Hysteroscopic myomectomy

One Cochrane review on fibroids only compared the laparoscopic with the laparotomic approach (Griffiths et al., 2006). We excluded an RCT (Seracchioli et al., 2000) from this SR since patients with submucous fibroids were not included.

We identified one additional RCT on pregnancy outcome in subfertile patients after myomectomy compared with expectant

Table II Outpatient hysteroscopy in recurrent IVF failure

Reference	Demirool and Gurgan, 2004	Rama Raju et al., 2006
Method of randomization	Computer-generated list	Computer-generated list
Concealment	Yes	Not clear
Blinding	No	Yes
Groups comparable	Yes	Yes
Intention-to-treat analysis	Yes	Yes
Follow-up rate analysis	>95%	>95%
Number of included patients	421	520
Type of infertility	Primary	Primary
Previous investigations	HSG	HSG
IVF history	≥2 failed cycles	≥2 failed cycles
Timing of hysteroscopy	Follicular phase	Follicular phase
Distension medium	Saline	Glycine
% Abnormal findings	26%	37%
Intervention	5 mm hysteroscopy (n = 210)	5 mm hysteroscopy (n = 265)
Control	No hysteroscopy (n = 211)	No hysteroscopy (n = 255)
Outcome measure	Clinical pregnancy rate, miscarriage rate	Clinical pregnancy rate, miscarriage rate, live birth rate

management (Casini et al., 2006). From an undefined cohort of women referred to a university fertility centre between January 1998 and April 2005, 193 patients suffered from unexplained subfertility and had an ultrasonographic diagnosis of fibroids, fulfilling the inclusion criteria. All patients were younger than 35 years, and there had to be unexplained subfertility for more than 1 year, except for the presence of one knot (it has not been possible to obtain the exact definition of the term 'knot' as stated in the primary article) and/or fibroid smaller than 4 cm diagnosed by TVUS. It was not reported whether these patients suffered from other gynaecological symptoms such as menorrhagia or pain. The authors randomized 181 patients to surgical treatment (laparotomy and/or operative hysteroscopy) or expectant management. Patients who were randomized to undergo surgical treatment were asked to abstain from having sexual intercourse for 3 months after the surgical procedure before having timed intercourse. Patients in the expectant management group were asked to start having timed intercourse immediately after randomization.

Only the data of patients with submucous fibroids (n = 94) with or without intramural fibroids were used in the present SR; the study

characteristics are presented in Table I. It is unclear whether all patients were systematically examined by hysteroscopy to confirm or exclude submucous fibroids. Nor is it clear whether only intramural fibroids with uterine cavity deformation were included or not. Pregnancy was defined as the visualization of an embryo with cardiac activity at 6–7 weeks of pregnancy. At 12 months after randomization, pregnancy rates were almost doubled after removal of fibroids in patients with submucous fibroids with or without intramural fibroids. The difference was however only marginally significant according to our calculation, in contrast to the authors' report (RR = 1.9; 95% CI: 1.0–3.7) (Fig. 2b). The NNT to gain one additional conception is 5 but there is a considerable variation in the CI (NNT = 5; 95% CI: 3–100). No significant differences in pregnancy rate were found after myomectomy compared with expectant management if the subgroup of subfertile patients included only those with submucous fibroids (RR = 1.6; 95% CI: 0.7–3.5). Our calculation was again in conflict with the authors' report where a statistically significant difference was reported in this subgroup.

Hysteroscopic metroplasty

We found two RCTs on hysteroscopic metroplasty but excluded one owing to lack of data on reproductive outcome (Vercellini et al., 1993). The other RCT compared two methods of hysteroscopic treatment of uterine septa (resectoscopy versus Versapoint electrode) in a mixed population of 160 patients with subfertility and recurrent pregnancy loss (Colacurci et al., 2007). The study characteristics are presented in Table I. There was no difference in pregnancy rates after hysteroscopic septoplasty with the Versapoint electrode or the resectoscope (RR = 1.1; 95% CI: 0.7–1.9). Clinical pregnancy rate was defined by rising hCG levels and visualization of a gestational sac. We calculated the data on reproductive outcome in the subgroup of patients with subfertility compared with those with recurrent pregnancy loss. There were significantly fewer pregnancies after hysteroscopic metroplasty in the subfertile subgroup (RR = 0.7; 95% CI: 0.5–0.9). The NNT to gain one additional pregnancy in the subfertile group compared with the recurrent pregnancy loss population is 4 (NNT = 4; 95% CI: 3–14). Because it was unknown which patients with recurrent pregnancy loss also suffered from subfertility, formal interaction was not studied.

Hysteroscopic synechiolysis

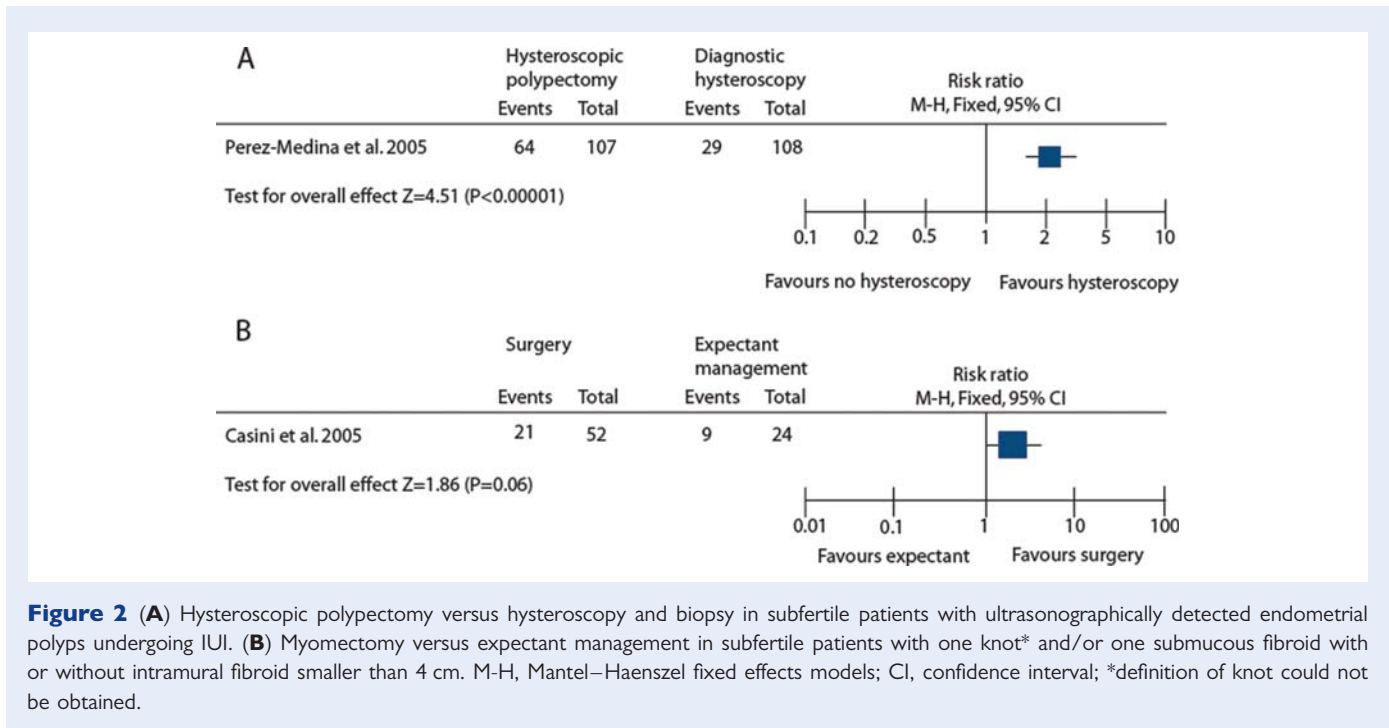
No randomized trials were retrieved on pregnancy rates after hysteroscopic synechiolysis in subfertile patients with intrauterine adhesions compared with expectant management.

To the best of our knowledge there are no controlled studies.

Does diagnostic or operative hysteroscopy increase the pregnancy rate in subsequent IVF cycles in subfertile patients undergoing IVF?

Two RCTs that investigated the effectiveness of hysteroscopy prior to IVF (Demirool and Gurgan, 2004; Rama Raju et al., 2006) were identified. The quality of these RCTs, the study characteristics, and the patient and intervention characteristics are summarized in Table II.

Overall 941 patients with at least two failed IVF attempts scheduled to undergo additional IVF treatment in two tertiary non-university IVF



clinics were included. All patients had primary subfertility and a normal uterine cavity on hysterosalpingography (HSG). They were randomized into two groups using computer-generated random numbers to study the effect of the intervention (office hysteroscopy) on pregnancy outcome. Group I ($n = 476$) did not undergo an office hysteroscopy prior to IVF treatment. In group II ($n = 465$) office hysteroscopy was performed with a 5 mm 30° hysteroscope. Group II was subdivided into group IIa with normal findings ($n = 314$) and group IIb with uterine pathology ($n = 151$), which was treated during the same procedure.

Office hysteroscopy immediately prior to a next IVF cycle significantly increased the clinical pregnancy rate compared with patients where a subsequent IVF cycle was started without prior hysteroscopy (RR = 1.6; 95% CI: 1.3–1.9) (Fig. 3). Clinical pregnancy was defined by visualization of fetal heart pulsation at 6 weeks. The NNT to gain one additional pregnancy is 7 (NNT = 7; 95% CI: 5–12).

In the intervention group, there was no significant difference in treatment effect between women with normal findings ($n = 314$) and women with uterine pathology ($n = 151$) (RR = 1.0; 95% CI: 0.7–1.2). However, as it was unknown which patients in the control group had intrauterine pathology, formal interaction was not studied.

Discussion

Polyps

The RCT detailing the effectiveness of hysteroscopic polypectomy in subfertile patients with endometrial polyps treated subsequently with IUI (Pérez-Medina et al., 2005) gives apparently straightforward results. This does not necessarily establish a causal link between endometrial polyps in general and subfertility. Moreover, absence of blinding may be an alternative explanation for the higher pregnancy rates

after polypectomy (Ankum, 2005). Since the number of patients treated by laparoscopy was not stated, we suggest that differences in undetected and untreated pelvic pathology such as endometriosis could also have introduced bias.

Since non-controlled studies fail to present consistent results concerning the effectiveness of hysteroscopic polypectomy (Valle, 1984; Hereter et al., 1998; Varasteh et al., 1999; Spiewankiewicz et al., 2003; Batioglu and Kaymak, 2005; Annan and Amoah, 2006; Kassab et al., 2007), no firm recommendations can be given based on the results and conclusions of this single randomized trial.

The observation from non-controlled trials that pregnancy rates are higher after removal of tubocornual polyps than after removal of polyps situated in other intrauterine locations suggests that tubocornual polyps may have a different effect on reproductive function (Venturini et al., 1987; Brooks et al., 1990; Lee et al., 1997; Shokeir et al., 2004; Yanaiharu et al., 2008). Other investigators have suggested a possible association between endometrial polyps and endometriosis (McBean et al., 1996; Kim et al., 2003). We hypothesize that tubocornual polyps, especially when bilaterally present and large, may preferentially interfere with oocyte/embryo transport. Moreover, they may protect (through a valve mechanism) against retrograde menstruation and possibly pelvic endometriosis. Polyps in the isthmocervical part of the uterus may preferentially interfere with sperm transport and may facilitate retrograde menstruation through a similar valve mechanism, obstructing the outflow tract. These two hypothetical mechanisms could explain the differences in conception rates after hysteroscopic removal of polyps in different locations as observed in non-controlled studies but need further research in the future.

Fibroids

The impact of fibroids on fertility remains controversial (Pritts, 2001; Lefebvre et al., 2003; Vilos, 2003; Griffiths et al., 2006; Somigliana

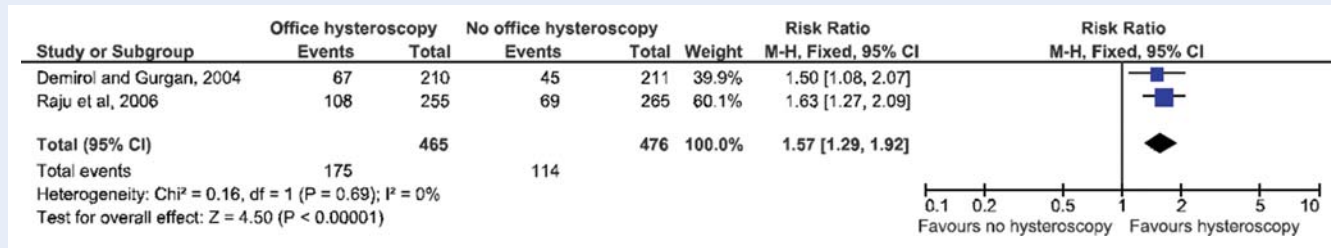


Figure 3 Hysteroscopy versus no hysteroscopy in patients with at least two failed IVF attempts.

et al., 2007; Vimercati et al., 2007; Klatsky et al., 2008; Somigliana et al., 2008; Pritts et al., 2009).

The only randomized trial comparing myomectomy to expectant management in patients with fibroids and subfertility (Casini et al., 2006) was underpowered and not blinded. It is unclear whether hysteroscopy has been performed systematically in all patients. The inclusion criterion 'knot' is not defined and is troublesome. Moreover, our interpretation of data did not match that of the authors, as we found only a marginally beneficial effect of myomectomy versus expectant management.

Observational epidemiological studies aimed at elucidating the causal relationship between fibroids and infertility are also inconclusive (Seoud et al., 1992; Narayan and Goswamy, 1994; Farhi et al., 1995; Lumbiganon et al., 1996; Eldar-Geva et al., 1998; Marshall et al., 1998; Ramzy et al., 1998; Stovall et al., 1998; Bulletti et al., 1999; Bajekal and Li, 2000; Dietterich et al., 2000; Healy, 2000; Hart et al., 2001; Jun et al., 2001; Surrey et al., 2001; Wang et al., 2001; Check et al., 2002; Donnez and Jadoul, 2002; Ng and Ho, 2002; Yarali and Bukulmez, 2002; Bulletti et al., 2004; Manyonda et al., 2004; Oliveira et al., 2004; Parazzini et al., 2004; Wang and Check, 2004; Wise et al., 2004; Benecke et al., 2005; Gianaroli et al., 2005; Ng et al., 2005; Rackow and Arici, 2005; Surrey et al., 2005; Khalaf et al., 2006; Klatsky et al., 2007). Overall the studies are often non-controlled or controlled retrospectively, sample size is usually small and data analysis often lacks correction for important confounding variables such as maternal age.

Since the randomized trial on fibroids included only patients with one knot and/or one fibroid smaller than 4 cm, a size effect relationship can hardly be demonstrated. Non-controlled studies have suggested that the number, size and distortion effect of fibroids on the uterine cavity may be important (Bulletti et al., 1999; Varasteh et al., 1999; Bernard et al., 2000; Fernandez et al., 2001; Oliveira et al., 2005; Khalaf et al., 2006; Mukhopadhaya et al., 2007).

The precise mechanism through which fibroids interfere with human reproduction is still unknown. Fibroids are believed to interfere with sperm migration, ovum transport and embryo implantation (Richards et al., 1998). This may be caused by altered contours of the uterine cavity resulting in altered mechanical pressure or abnormal uterine contractility (Bettocchi et al., 2002; Farrugia et al., 2002; Oliveira et al., 2004). Local inflammation caused by the presence of submucous fibroids may cause focal endometrial vascular disturbances, chronic endometritis or secretion of vasoactive substances. Even an enhanced intrauterine androgen environment impairing gamete or zygote transport and embryo implantation has been suggested (Richards et al., 1998). It is biologically plausible that fibroids

localized near the cervix may interfere with sperm transport, whereas tubocornual fibroids may preferentially impair oocyte/embryo transport (Oliveira et al., 2004).

Besides the subfertility problem, other factors should also be taken into consideration in the management of submucous fibroids. A large proportion of these patients also suffer from other gynaecological symptoms such as pain, menorrhagia or recurrent pregnancy loss.

Moreover, large fibroids are also associated with other pregnancy complications, such as premature labour or abnormal fetal presentation. However, in the absence of randomized trials on the subject one should be cautious with interventions outside the context of a randomized clinical trial.

Septate uterus

Hysteroscopic metroplasty is frequently performed in patients with recurrent miscarriage because a uterine septum is associated with an adverse pregnancy outcome. However, the effectiveness of hysteroscopic metroplasty in reducing miscarriage in patients with septate uterus is at present not demonstrated by randomized trials. A review of non-controlled studies suggests that the pregnancy outcome is more favourable after hysteroscopic metroplasty (Homer et al., 2000). However, the results of this review are biased by the fact that women with recurrent pregnancy loss treated by metroplasty served as their own controls (Christiansen et al., 2005). Although it could be considered unethical given that a hysteroscopic metroplasty is relatively easy to perform, a randomized trial is needed, and in fact is currently underway (<http://www.studies-obsgyn.nl/trust NTR 1676>). If the effectiveness of hysteroscopic removal of uterine septa in reducing the risk of recurrent miscarriage would be proven, this could lead to recommendations in subfertile patients undergoing expensive assisted reproduction treatments.

The precise mechanism through which a uterine septum may cause subfertility is not fully understood. It is biologically plausible that the endometrium of the septum may be unsuitable for blastocyst implantation. One author demonstrated that the morphological development of endometrial septal specimens is suboptimal, using scanning electron microscopy (Fedele et al., 1996). The association between septate uterus and endometriosis, as reported in some non-controlled studies, may explain the subfertility of at least some patients with septate uterus but requires further research (Fayez, 1986; Fedele et al., 1993; Grimbizis et al., 1998; Nawroth et al., 2006).

In counselling the individual patient with a uterine septum, the risks of other possible pregnancy complications, such as abnormal fetal

presentation or intrauterine growth retardation, should also be taken into consideration. Future trials on the subject should also study the course of pregnancy.

Intrauterine adhesions

Randomized or controlled studies on reproductive outcome after hysteroscopic synechiolysis are absent. The overall quality of the available non-controlled studies is very poor (Sugimoto, 1978; Schenker and Margalioth, 1982; Fedele et al., 1986; Friedman et al., 1986; Parent et al., 1988; Valle and Sciarra, 1988; Pistofidis et al., 1996; Mc Comb and Wagner, 1997; Pabuçcu et al., 1997; Roge et al., 1997; Protopapas et al., 1998; Capella-Allouc et al., 1999; Feng et al., 1999; Preutthipan and Linasmita, 2000; Zikopoulos et al., 2004; Kodaman and Arici, 2007; Yu et al., 2008). Moreover, the results cannot be directly compared since different non-validated classification systems of the severity of disease are used (American Fertility Society, 1988; Wamsteker et al., 1998; Nasr et al., 2000).

Subfertility in patients with intrauterine adhesions may be caused by complete or partial occlusion of the tubal ostia, uterine cavity or the cervical canal, preventing the migration of sperm or the implantation of the embryo. Severe destruction of the endometrium may also lead to defective or absent implantation.

In vitro fertilization

The higher pregnancy rates after hysteroscopy even in the absence of intrauterine pathology is a somewhat unexpected but biologically plausible observation. It is acceptable that cervical dilatation and/or direct hysteroscopic visualization of the uterine cavity facilitates embryo transfer (McManus et al., 2000; Mansour and Aboulghar, 2002). Moreover, an immunological mechanism triggered by the hysteroscopic manipulation or by the effect of the distension medium on the endometrium, similar to the increased odds of spontaneous pregnancy after HSG (Luttjeboer et al., 2007), might play a role. A new randomized trial on this subject is ongoing (Geslevich et al., 2006).

Summary conclusions and future research agenda

In patients with at least two failed IVF or ICSI attempts, simple diagnostic or operative hysteroscopy before a subsequent IVF or ICSI treatment is thought to improve reproductive outcome. Scarce evidence on the effectiveness of hysteroscopic surgery in subfertile women with polyps, fibroids, septate uterus or intrauterine adhesions suggests a potential benefit, but it is clear that more RCTs are needed before general recommendations can be given.

At present hysteroscopy should not be offered as a first-line investigation in all subfertile women despite its high patient compliance.

The role of hysteroscopic removal of intracavitary fibroids should be studied in asymptomatic patients with unexplained subfertility as well as in patients undergoing expensive IVF treatment. A randomized trial should measure the effectiveness of hysteroscopic metroplasty in reducing the risk of pregnancy loss in patients with at least two miscarriages, regardless of a co-existing problem of subfertility. The effectiveness of the newer anti-adhesive barrier agents as adjunctive therapy to hysteroscopic synechiolysis in patients with severe intrauterine adhesions should be addressed by a randomized trial. Finally, the role of

hysteroscopy before a first IVF attempt should be studied by a well-designed randomized trial.

Authors' Role

J.B. was responsible for coordinating the research and writing of this manuscript. S.W., P.P., C.P. and B.V.H. were involved in the selection of studies and the data extraction process. C.M. and T.D'H. were involved in the literature search in Leuven and review of the manuscript. B.W.M. and V.G. critically reviewed this SR.

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