Abstract

Recurrent implantation failure (RIF) may be due to unrecognized uterine pathology. Hysterosalpingography, transvaginal ultrasonography, saline infusion sonography and hysteroscopy are the tools to assess the inner architecture of the uterus. Hysteroscopy is considered to be the gold standard; however, the validity of hysteroscopy may be limited in the diagnosis of endometritis and endometrial hyperplasia. The frequencies of unrecognized uterine pathology revealed by hysteroscopy are 18–50% and 40–43% in patients undergoing IVF with or without RIF, respectively. Endometrial polyps may be associated with increased miscarriage rates. Implantation rates are decreased in patients with submucous or intramural fibroids with distorted uterine cavity. There is controversy on the impact of uterine septum less than 1 cm length on pregnancy outcome in IVF cycles. There is paucity of data on the role of hysteroscopy in failed IVF cycles. In the available two randomized controlled trials, pregnancy rates appear to be increased when hysteroscopy is performed; however within the hysteroscopy group, pregnancy rates are comparable among the normal or surgically corrected subgroups. Further studies are warranted to delineate the role of hysteroscopy in patients with failed IVF cycle(s). This review aims to evaluate the validity of office hysteroscopy in failed IVF cycles.

Keywords: assisted reproductive technologies, IVF, office hysteroscopy, recurrent implantation failure

Introduction

The presence of viable embryo(s), an anatomically and functionally receptive uterus and gentle embryo transfer are essential to achieve pregnancy in IVF cycles. Failure to conceive with IVF could be caused by many factors including inappropriate ovarian stimulation, suboptimal laboratory culture conditions and faulty embryo transfer technique. These would result in an overall low pregnancy rate for the IVF unit. However, even in successful units with high pregnancy rates, some couples may experience recurrent implantation failure (RIF).

Failure to conceive following 2–6 cycles, in which more than 10 high-grade embryos are transferred, is generally accepted as RIF (Dalton et al., 2006). RIF is heterogeneous and may be attributed to many factors that can be categorized to three main groups: (i) decreased endometrial receptivity; (ii) defective embryonic development; and (iii) factors with combined effect (e.g. endometriosis, hydrosalpinx) (Margalioth et al., 2006).

RIF might be due to unrecognized uterine pathology, and hysteroscopy is commonly employed in patients with RIF (Urman et al., 2005). In a survey of 65 IVF centres in the UK responding to a questionnaire aimed at delineating how they define and manage couples with RIF, hysteroscopy was employed in 70% of the centres (Tan et al., 2005). Various benign intrauterine pathologies such as endometrial polyp, intrauterine synechiae, uterine septum, myoma, endometritis and endometrial hyperplasia may have a negative effect on pregnancy rates in IVF. It is, therefore, essential to assess the anatomical integrity of the uterus before IVF. The tools that are currently used to assess the inner architecture of the uterine cavity are hysterosalpingography (HSG), transvaginal...
ultrasonography, saline infusion sonography (SIS) and office hysteroscopy. Of the available four diagnostic tools, office hysteroscopy is considered to be the gold standard (Bettocchi et al., 2004). Office hysteroscopy can be performed without general anaesthesia in an ambulatory setting with low cost, minimal morbidity and inconvenience to the patient (Marana et al., 2001). Furthermore, it gives the opportunity to correct the majority of the pathologies at the same time.

There is no doubt that hysteroscopy should be performed when there is suspicion of intrauterine pathology at transvaginal ultrasonography, SIS or HSG. However, even when no abnormality is found with these tools, at hysteroscopy several subtle intrauterine pathologies have been noted in 18–50% of patients undergoing IVF (Shamma et al., 1992; Doldi et al., 2005). There are currently three policies regarding the employment of hysteroscopy before IVF: (i) suspicion of intrauterine pathology at HSG, transvaginal ultrasonography or SIS; (ii) failed IVF cycle(s) despite normal HSG, transvaginal ultrasonography or SIS; and (iii) routine employment for all patients.

In order to delineate the role of hysteroscopy in failed IVF cycle(s), four relevant questions should be discussed.

**When and which diagnostic method(s) of varying accuracy have been used prior to recurrent implantation failure?**

Frequently, HSG is performed during the course of infertility work-up before IVF. The limited validity of HSG may, at least in part, be due to the poor technique that is often employed while performing the procedure (Gomel and Yarali, 1992).

With hysteroscopy considered as the gold standard, HSG has high sensitivity (81–98%), low specificity (23–35%), high false-negative (10–90%) and high false-positive (22–44%) rates (Golan et al., 1992; Preuthiphan and Linasmita, 2003; Roma Dalfo et al., 2004). Therefore, unless it is deemed necessary to perform during prior infertility work-up, HSG is not accepted as a valid tool to assess the inner architecture of the uterus before IVF.

Transvaginal ultrasonography, especially when performed during the late follicular phase, provides excellent imaging of the uterus and of endometrial abnormalities (Shaley et al., 2000). Endometrial polyps, submucosal myomas and uterine septae have typical ultrasonographic appearance. When hysteroscopy is considered to be the gold standard, the sensitivity, false-positive rate and positive predictive value were reported to be 99%, 6% and 94%, respectively (Narayan and Goswamy, 1993). The positive predictive values for specific abnormalities were 99% for intrauterine adhesions, 92% for submucous fibroids, 91% for endometrial polyps, 86% for endometritis and 86% for irregular endometrium. In concordance with the study by Narayan and Goswamy, the sensitivity and positive predictive value of transvaginal ultrasonography for detection of polyps, myoma and septum have been reported to be 71% and 100%, 100% and 100%, 100% and 100%, respectively in another study (Shaley et al., 2000). These data demonstrate that high-resolution ultrasonography, in experienced hands, is very valuable in detecting intrauterine pathologies.

Intrauterine adhesions may be difficult to diagnose at transvaginal ultrasonography. Small, irregular, hyperechoic structures interrupting the continuity of the endometrial layer should raise the suspicion of intrauterine synechiae (Shaley et al., 2000). When hysteroscopy is considered to be the gold standard, the sensitivity and positive predictive value of transvaginal ultrasonography for detection of synechiae have been reported to be 80% and 100% (Shaley et al., 2000). Positive predictive value of 99% has been reported in diagnosis of intrauterine synechiae in another study (Narayan and Goswamy, 1993). However, in two other studies (Soares et al., 2000; Oliveira et al., 2003), poor performance of transvaginal ultrasonography was noted. None of the six cases with RIF and documented to have intrauterine synechiae at hysteroscopy was suspected at transvaginal ultrasonography (Oliveira et al., 2003). None of the four cases with intrauterine synechiae were suspected at transvaginal ultrasonography and there were three false-positive diagnoses in another study (Soares et al., 2000).

Intrauterine synechiae is most commonly due to post-abortal curettage or prior uterine surgery and rarely due to genital tuberculosis. Adhesion formation occurs in 7–30% of patients after post-abortal curettage (Schenker and Margalioth, 1982; Kodaman and Arici, 2007). The role of infection, without uterine instrumentation, in the development of intrauterine synechiae is controversial (Polishuk et al., 1975, 1977). However, genital tuberculosis remains a significant cause of severe intrauterine adhesions, often producing complete obliteration of the uterine cavity with frequent recurrence of adhesions after hysteroscopic treatment (Bukulmez et al., 1999). The risk of intrauterine adhesion in a patient with no history of uterine curettage, uterine surgery or genital tuberculosis may be very low.

The use of contrast media such as saline with transvaginal ultrasonography may improve the delineation of uterine cavity abnormalities (Ayida et al., 1997). In a study of 44 patients undergoing IVF, the validity of SIS was assessed, taking hysteroscopy as the gold standard (Ayida et al., 1997). SIS had 88% sensitivity, 100% specificity, 100% positive predictive value and 92% negative predictive value. It has been reported to have better accuracy than transvaginal ultrasonography for the diagnosis of all types of intrauterine pathologies; the sensitivity, specificity, positive predictive value and negative predictive value of SIS have been reported to be 98%, 94%, 95% and 98%, respectively (Ragni et al., 2005). Thus, in experienced hands, SIS may be an easy, safe, and well-tolerated alternative to diagnostic hysteroscopy in the initial evaluation of the uterine cavity.

Hysteroscopy is generally considered to be the gold standard in the diagnosis of intrauterine pathology, including endometrial polyp, submucous myoma, intrauterine synechiae and uterine septum. However, the validity of hysteroscopy in the diagnosis of chronic endometritis and endometrial hyperplasia may be limited, in which case endometrial biopsy is considered to be the gold standard (Clark et al., 2002; Polisseni et al., 2003). In a prospective controlled study enrolling 2190 patients undergoing hysteroscopy (Cicinelli et al., 2008), 438 were diagnosed to have chronic endometritis when thick, oedematous and hyperaemic endometrial mucosa covered by micropolyps (less than 1 mm
in size) were noted at hysteroscopy. When the findings of hysteroscopy were compared with histological examination, hysteroscopy was found to have a positive predictive value of 89%. In another study on the diagnosis of endometrial hyperplasias, the sensitivity, specificity, positive predictive value and negative predictive value of hysteroscopy were noted to be 56%, 89%, 48% and 92%, respectively when histopathology was taken as the gold standard (Lasmur et al., 2006).

**What is the frequency of unsuspected intrauterine pathologies before IVF?**

### Patients without recurrent implantation failure

There is paucity of data on the frequency of unrecognized uterine pathology that will duly be discovered by routine hysteroscopy in patients scheduled to undergo IVF. In 300 patients scheduled to undergo IVF, the frequency of unsuspected intrauterine pathology has been reported to be 40% by routine hysteroscopy (Doldi et al., 2005); all 300 patients had normal HSG within the previous 12 months and normal ultrasonography within the previous 2 months. The types and frequencies of the subtle pathologies were as follows: endometrial polyps = 78 (65%), endometrial hyperplasia = 20 (17%), endometrial hypotrophia = 16 (13%), and other (endometritis, adhesions) = six (5%). In another study, despite normal HSG, an abnormality was noted in 12/28 (43%) of the patients at hysteroscopy before IVF (Shamma et al., 1992) including small uterine septa, small submucous fibroids, uterine hypoplasia and cervical ridges.

### Patients with recurrent implantation failure

The frequency of unrecognized intrauterine pathologies in patients with RIF varies between 18 and 50% (Goldenberg et al., 1991; Kirsop et al., 1991; Dicker et al., 1992; La Sala et al., 1998; Schiano et al., 1999; Oliveira et al., 2003; Demirol and Gürgan, 2004; Rama Raju et al., 2006). The definition of RIF in all these studies was implantation failure in two IVF cycles (Goldenberg et al., 1991; La Sala et al., 1998; Schiano et al., 1999; Oliveira et al., 2003; Demirol and Gürgan, 2004; Rama Raju et al., 2006) or gamete intra-Fallopian transfer (GIFT) cycles (Kirsop et al., 1991) with more than two good quality embryos transferred per attempt.

**Is there any detrimental effect of subtle intrauterine pathologies on pregnancy rates in IVF?**

There is lack of good evidence on the impact of subtle intrauterine pathologies on IVF outcome (Cohen et al., 2007). Endometrial polyps are not infrequently encountered in infertile women. There is paucity of data on the impact of diameter, localization and number of endometrial polyps on spontaneous fertility. Hysteroscopic removal of endometrial polyps appears to improve spontaneous pregnancy rates in women with otherwise unexplained infertility (Varasteh et al., 1999; Shokeir et al., 2004; Stamatellos et al., 2008). However, no statistical difference in spontaneous fertility rates has been noted between patients undergoing hysteroscopic removal of polyps <1 cm in diameter and >1 cm diameter or multiple polyps (Stamatellos et al., 2008). In a recent study, excision of polyps located at the utero–tubal junction was associated with a significantly higher pregnancy rate compared with localization to posterior, anterior or lateral uterine walls (Yanaihara et al., 2008).

The impact of endometrial polyps less than 2 cm in size on IVF outcome was studied in 83 patients (Lass et al., 1999). Forty-nine women underwent fresh IVF and embryo transfer with the polyp (Group I). In the remaining 34 women, hysterectomy and polypectomy were performed immediately following oocyte retrieval and the suitable embryos were all frozen and the replacement was made a few months later (Group II). The pregnancy rate of Group I was similar to the general pregnancy rate of the Unit over the same time period (22% vs 23%, respectively); however, the miscarriage rate was higher, although the difference did not reach statistical significance (27% vs 11%). In Group II, the pregnancy and miscarriage rates were similar to those of the general frozen embryo cycles of the unit (30% and 14% versus 22% and 12%, respectively). The authors concluded that, although polypectomy less than 2 cm does not increase the pregnancy rate significantly, it might improve the take-home baby rate in patients undergoing IVF.

In a randomized controlled trial, the effect of endometrial polyps on pregnancy rates in intrauterine insemination (IUI) cycles was evaluated in 215 women (Perez-Medina et al., 2005). Four rounds of IUI were performed, with the first IUI planned to be at three cycles after hysteroscopy. Hysteroscopic polypectomy was performed in 101 women and diagnostic hysteroscopy (with polyp biopsy) was performed in the remaining 103. Eleven patients were excluded from the study; six from the polypectomy (three lost to follow-up, two pathologic reports of submucosal myoma and in one patient in whom the polyp was not confirmed) and five in the diagnostic hysteroscopy group (one lost to follow-up, two patients in whom the polyp was not confirmed and two pathologic reports of myoma). The respective cumulative pregnancy rates were 65% and 28% (P < 0.001). Pregnancies in the polypectomy group were obtained before the first IUI in 65% of the cases. No relationship was noted between the size of the polyp and the chance of pregnancy. The authors concluded that hysteroscopic polypectomy should be considered in an infertile woman with otherwise unexplained infertility. Achieving spontaneous pregnancies after polypectomy may suggest a strong cause–effect relationship of the polyp in the implantation process.

The effect of minor residual septum (<1 cm) on reproductive outcome is controversial (Grimbizis et al., 2001; Fedele et al., 2006). Following hysteroscopic incision of the uterine septum, a residual septum may be noted in 38–44% of the cases, depending mainly on the experience of the surgeon (Fedele et al., 1996; Kormanyos et al., 2006). No detrimental effect of a residual septum of <1 cm was noted in one study; the cumulative spontaneous live birth rates at 18 months were 28% and 36% in the residual and no-residual septum groups, respectively (Fedele et al., 1996). However, in a more recent study, the septum was completely removed during the first hysteroscopy in 58 women (62%); a residual septum was noted in 36 women (38%) (Kormanyos et al., 2006). Subsequent incision of the septum was performed in cases with repeated miscarriage or
failure to conceive (29/36, 81%). The difference in delivery rate after the first hysteroscopy between those with a normalized uterine cavity (26/58, 45%) and those with remnants (7/36, 19%) was statistically significant (P < 0.05). The authors concluded that women with a remnant uterine septum have an increased chance of successful pregnancy with an improved obstetric outcome after normalization of the cavity. In a retrospective study evaluating the impact of an incomplete uterine septum on IVF outcome, similar pregnancy rates were noted following incision of the incomplete septum compared with a group with normal uterine cavity (Ozgur et al., 2007).

As far as is known, there are no data on the impact of minor-moderate adhesions on IVF outcome. Submucous fibroids are usually symptomatic, easily suspected at transvaginal ultrasonography and therefore resected by hysteroscopy before IVF. The impact of those not suspected, small submucous fibroids on IVF outcome is not clear. Treatment outcome of 106 IVF or intracytoplasmic sperm injection (ICSI) cycles in 88 patients with uterine fibroids (33 subserosal, 46 intramural without cavity distortion, and nine submucosal) was compared with that of 318 IVF/ICSI cycles in age-matched controls without fibroids (Eldar-Geva et al., 1998). The pregnancy and implantation rates of the patients with subserosal, intramural without cavity distortion, submucosal fibroids and controls were 34%, 16%, 10%, 30% and 15%, 6%, 4%, 16%, respectively. Both pregnancy and implantation rates were significantly lower in the presence of submucosal or intramural fibroids without cavity distortion, when compared with the subserous and control groups.

### What is the quality of evidence of liberal hysteroscopy in patients with recurrent implantation failure?

There are four studies evaluating the role of hysteroscopy following failed IVF cycles (Schiano et al., 1999; Oliveira et al., 2003; Demirol and Gürgan, 2004; Rama Raju et al., 2006) (Table 1). In a retrospective study, the role of re-hysteroscopy was evaluated in 73 women who had two IVF implantation failures (Schiano et al., 1999). In half of the cases, an abnormality was discovered. A pregnancy rate of 22% was noted following correction of intrauterine pathologies.

In a prospective observational study, hysteroscopic findings in 55 patients undergoing IVF who repeatedly failed to conceive despite transfer of two good quality embryos were assessed (Oliveira et al., 2003). All patients had a normal uterine cavity on hysteroscopy performed within 1 year. In 25 patients (45%) an abnormality was noted at hysteroscopy; submucous fibroid (n = 2), polyp (n = 10), adhesions (n = 6), endometritis (n = 7). A previous transvaginal ultrasonography raised suspicion of abnormalities in 13 patients (three of 30 without abnormalities and 10 of 25 with abnormalities). Abnormalities not seen on ultrasonography were found at hysteroscopy in 15 of 25 patients with abnormalities. Following correction of the pathology, all patients underwent a third IVF cycle. Pregnancy (50% versus 20%) and implantation (19% versus 6%) rates were significantly higher in patients who were treated for uterine abnormalities than in patients who had normal uterine cavity on hysteroscopy. The authors concluded that the incidence of unrecognized pathologies is high in patients with implantation failure and hysteroscopy should be applied in all such cases.

The role of hysteroscopy in RIF was assessed in two randomized controlled trials (Demirol and Gürgan, 2004; Rama Raju et al., 2006). A total of 421 patients who had two or more failed IVF cycles were prospectively randomized to no-office hysteroscopy (Group I; n = 211) and office hysteroscopy (Group II; n = 210) groups (Demirol and Gürgan, 2004). All 421 patients had normal HSG. Office hysteroscopy was normal in 154 patients (73%; Group IIa). An abnormality was noted at hysteroscopy in 56 (27%; Group IIb) patients, including endometrial polyp (n = 33), filmy and mild adhesions (n = 18) and cervical adhesion (n = 5). All intrauterine pathologies were corrected at the time of hysteroscopy. No significant difference existed among the three groups (Groups I, IIa, IIb) regarding female age, mean number of prior failed IVF cycles, number of oocytes retrieved, fertilization rate and number of embryos transferred. The clinical pregnancy rates of Groups I, IIa and IIb were 22%, 33% and 30%, respectively (P < 0.05 for Group I versus Group IIa and Group I versus Group IIb). The miscarriage rates of the three groups were comparable. The authors concluded that routine hysteroscopy should be performed in failed IVF cycles.

In another randomized controlled trial with a very similar study design, 520 patients with normal HSG and two or more failed IVF cycles with two or more good quality embryos transferred per procedure were randomized to no-hysteroscopy (n = 265) and

### Table 1. Quality of evidence of the effectiveness of hysteroscopy on clinical pregnancy rate following failed IVF cycles.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>n</th>
<th>No hysteroscopy group</th>
<th>Hysteroscopy group Surgically corrected</th>
<th>Surgical correction</th>
<th>Normal pregnancy rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schiano et al., 1999</td>
<td>Retrospective</td>
<td>73</td>
<td>N/A</td>
<td>22</td>
<td>N/A</td>
<td>50%</td>
</tr>
<tr>
<td>Oliveira et al., 2003</td>
<td>Prospective observational</td>
<td>55</td>
<td>N/A</td>
<td>50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>20&lt;sup&gt;a&lt;/sup&gt;</td>
<td>88%</td>
</tr>
<tr>
<td>Demirol and Gürgan, 2004</td>
<td>Randomized controlled trial</td>
<td>210</td>
<td>22&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>30&lt;sup&gt;b&lt;/sup&gt;</td>
<td>33&lt;sup&gt;b&lt;/sup&gt;</td>
<td>106%</td>
</tr>
<tr>
<td>Rama Raju et al., 2006</td>
<td>Randomized controlled trial</td>
<td>255</td>
<td>26&lt;sup&gt;ab&lt;/sup&gt;</td>
<td>37&lt;sup&gt;b&lt;/sup&gt;</td>
<td>44&lt;sup&gt;b&lt;/sup&gt;</td>
<td>50%</td>
</tr>
</tbody>
</table>

<sup>a,b</sup>Values within rows with the same superscript are significantly different (P < 0.05).
hysteroscopy (n = 255) groups (Rama Raju et al., 2006). Office hysteroscopy was normal in 160 patients (63%; Group IIA). An abnormality was noted at hysteroscopy in 97 (38%; Group IIb) patients, including endometrial polyp (n = 34), cervical stenosis (n = 30), endometrial hyperplasia (n = 12), synchia (n = 12), sepatate uterus (n = 8) and fibroids (n = 1). All intrauterine pathologies were corrected at the time of hysteroscopy. No significant difference existed among the three groups (Groups I, IIA, IIb) regarding female age, mean number of prior failed IVF cycles, number of oocytes retrieved, fertilization rate and number of embryos transferred. The clinical pregnancy rates of Groups I, IIA and IIb were 26%, 44% and 40%, respectively (P < 0.05 for Group I versus Group IIA and Group I versus IIb). The miscarriage rates of the three groups were comparable. The authors concluded that routine hysteroscopy should be performed in failed IVF cycles.

The two randomized controlled trials (Demirol and Gürgan, 2004; Rama Raju et al., 2006) did not report whether the pathologies they noted at hysteroscopy were suspected or not at transvaginal ultrasonography. Since suspicion of intrauterine pathology at either transvaginal ultrasonography or SIS would dictate performing hysteroscopy before a new attempt of IVF, it would be more valuable to assess the role of hysteroscopy in patients with RIF but no suspicion of pathology at ultrasonography, SIS, HSG or a combination thereof. It is of interest that these two randomized controlled trials have a very similar study design as well as results, both report high pregnancy rates in patients with RIF who underwent office hysteroscopy and no pathology was found. It is also of interest that both randomized controlled trials are in conflict with the study by Oliveira et al. (2003), which observed significantly lower pregnancy rates in women with normal hysteroscopy that may stem from other factors contributing to RIF rather than the uterine factor.

Conclusions

Hysteroscopy is considered to be the gold standard to diagnose intrauterine pathology. The frequency of unsuspected intrauterine pathologies discovered by hysteroscopy in patients with RIF ranges from 18–50%. Heterogeneity of factors contributing to RIF and different patient inclusion criteria may stem from other factors contributing to RIF rather than the uterine factor.

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