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# ART and uterine pathology: how relevant is the maternal side for implantation?

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**BACKGROUND:** Assisted reproduction technology (ART) has become a standard treatment for infertile couples. Increased success rates obtained over the years have resulted primarily from improved embryo quality, but implantation rates still remain lower than expected. The uterus, an important player in implantation, has been frequently neglected. While a number of uterine pathologies have been associated with decreased natural fertility, less information exists regarding the impact of these pathologies in ART. This report reviews the evidence to help clinicians advise ART patients.

**METHODS:** An electronic search of PubMed and EMBASE was performed to identify articles in the English, French or Spanish language published until May 2014 which addressed uterine pathology and ART. Data from natural conception were used only in the absence of data from ART. Studies were classified in decreasing categories: RCTs, prospective controlled trials, prospective non-controlled trials, retrospective studies and experimental studies. Studies included in lower categories were only used if insufficient evidence was available. Pooled data were obtained from systematic reviews with meta-analyses when available. The summary of the evidence for the different outcomes and the degree of the

recommendation for interventions were based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) statement recommendations.

**RESULTS:** There is strong evidence that surrogacy is effective for uterine agenesia. For the remaining pathologies, however, there is very little evidence that the established treatments improve outcomes, or that these pathologies have a negative effect on ART. In the presence of an apparently normal uterus, assessing endometrial receptivity (ER) is the goal; however diagnostic tests are still under development.

**CONCLUSIONS:** The real effect of different uterine/endometrial integrity pathologies on ART is not known. Moreover, currently proposed treatments are not based on solid evidence, and little can be done to assess ER in normal or abnormal conditions. No strong recommendations can be given based on the published experience, bringing an urgent need for well-designed studies. In this context, we propose algorithms to study the uterus in ART.

**Key words:** assisted reproduction / endometrial receptivity / endometrium / implantation / uterus

# Introduction

Assisted reproduction technology (ART) has become a routine way to treat infertile couples. Although initially developed with the aim of treating tubal infertility, it soon became apparent that ART could be employed in almost all other types of infertility. Many improvements have been introduced to make ART cycles more successful, including better culture conditions, different selection criteria for the best embryos for transfer, and extending embryo culture to the blastocyst stage.

Despite clear breakthroughs in ART outcomes, implantation is still considered the 'black box' of ART. In international reports, pregnancy rates (PRs) range between 19 and 39% in *in vitro* fertilization (IVF) (Zegers-Hochschild *et al.*, 2014). In the best case scenario for patients with a good prognosis and embryo selection, PRs still only reach 61–70% (Gardner *et al.*, 2004; Yang *et al.*, 2012). These results suggest that the uterus itself might play a more important role than previously considered.

The idea that a good embryo can implant anywhere comes from reports showing ectopic pregnancies in hysterectomized women (Fylstra, 2010). However, it is known, for instance, that age affects endometrial receptivity (ER) in oocyte donation (OD) cycles (Reis Soares *et al.*, 2005). Moreover, there are different uterine pathologies, easily diagnosed with current imaging methods during the infertility work-up, that have been associated with impaired natural fertility in women. In general, evidence from which a clinician can make good decisions in the context of ART is scarce.

This review aims to highlight the importance of the uterus, and uterine pathologies in particular, in women undergoing ART. Our starting points are those patients undergoing an ART cycle where the uterine factor is routinely evaluated by transvaginal sonography (TVS) and some pathology is found. Our goal is to describe the various problems that a clinician may face, and to suggest appropriate solutions based on the available literature. In addition, unsuccessful repeated ART cycles, referred to as repeated implantation failure, are also observed for many women where the uterus appears to be morphologically normal. With this information, we finally propose an approach to study the uterus in order to improve ER and ART outcomes.

# Methods: search strategy

An electronic search in PubMed and EMBASE was performed to identify articles published in the English, French or Spanish language dealing with uterine pathology and ART interventions (the search strategy is shown in Supplementary Data). Randomized and prospective studies were also searched for in clinicaltrials.gov and the Cochrane database, but they were only included if they had published results. The bibliography of the retrieved articles was used to identify other potentially relevant literature. This review includes literature published any time prior to May 2014.

Original studies were classified into five decreasing categories: randomized controlled trials (RCTs), prospective controlled trials, prospective non-controlled trials, retrospective studies and experimental studies. Studies included in lower categories were only used if enough evidence was not provided by high-quality studies. This review describes ART outcomes in the presence of different uterine pathologies. Data on natural conception have been discussed only in the case that no experience with ART has been reported. Pooled data were obtained from systematic reviews with meta-analysis when available. Reports in the form of abstracts were not considered.

The primary outcome used to indicate success has been live birth rates. However, many studies report other secondary outcomes, such as implantation rates (IRs) or PRs that have been employed in the absence of live birth rates. The summary of the evidence for the different outcomes and the degree of the recommendation for interventions analyzed in this review are based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) statement recommendations (Guyatt *et al.*, 2008).

# The abnormal uterus

The embryo adheres to and penetrates the endometrium during the implantation process, forming a whole and unique structure which will result in a live birth after an orchestrated series of relevant events (Cha *et al.*, 2013). Therefore, a morphologically normal endometrium is of prime importance for sustaining a pregnancy to term. Understanding ER is the subject of much investigation, with sonographic evaluation of the endometrium representing one widely employed method in ART.

## Endometrial lining

The use of ultrasound to predict uterine implantation has grown in recent decades due to the employment of high-resolution ultrasonographic technology. The endometrial thickness (Alam *et al.*, 1993; Friedler *et al.*, 1996), endometrial pattern (Coulam *et al.*, 1994), color Doppler

(Coulam *et al.*, 1994) and volume (Schild *et al.*, 2001) have been assayed as non-invasive markers of ER.

*Endometrial thickness* (Eth)—the distance between the echogenic interfaces at the junction of endometrium and myometrium, measured in the midsagittal section during TVS—is one of the most frequently employed indirect predictors of ER. Several studies have reported a correlation between Eth and the potential of the embryos to implant (Sher *et al.*, 1991; Rinaldi *et al.*, 1996; Zhang *et al.*, 2005; van Gestel Traub *et al.*, 2009), while others have found no such correlation (Alam *et al.*, 1993; Remohi *et al.*, 1997; Leibovitz *et al.*, 1999; De Geyter *et al.*, 2000; Schild *et al.*, 2001; Puerto *et al.*, 2003).

The prevalence of an 'abnormal' or 'thin' endometrium varies with age, being present in 5% of younger women undergoing either IVF (Sher *et al.*, 1991) or OD (Remohi *et al.*, 1997), and increasing to 25% in older patients (Sher *et al.*, 1991).

Specific cut-off values defining 'normal' and 'thin' endometrium have not been identified. Successful implantation has been reported with minimum Eth threshold values of 4–5 mm (Remohi *et al.*, 1997; Check *et al.*, 2003; Check and Cohen, 2011) and 6 mm (Alam *et al.*, 1993), demonstrating that a thin endometrium does not necessarily exclude the chance of pregnancy. Others have reported a cut-off thickness of 7 mm as appropriate for implantation (Friedler *et al.*, 1996). Moreover, a number of studies have found increased IRs and PRs when the Eth is >9 mm (Zhang *et al.*, 2005; Richter *et al.*, 2007), >10 mm (Rinaldi *et al.*, 1996), or between 9 and 14 mm (Check *et al.*, 2004).

On the other end, the incidence of an endometrium that is 'too thick', which may also negatively affect ART, varies from 5.3 to 11.6% in IVF (Dietterich *et al.*, 2002; Zhao *et al.*, 2012) and up to 21% in OD (Remohi *et al.*, 1997). Some groups found no relation between a 'too thick' (>14 mm) Eth and decreased IRs or PRs following ART (Dietterich *et al.*, 2002), where pregnancies were reported with an Eth of 19–20 mm (Quintero *et al.*, 2004; Zhao *et al.*, 2012).

These conflicting data are potentially due to the heterogeneity of studies, the relatively low number of analyzed cycles, the use of different ovarian stimulation protocols, the evaluation of Eth at different points in the cycle, or differing techniques of ultrasonographic examination.

The critical point, however, is that the minimum Eth required to attain implantation remains undefined. Remohi *et al.* (1997) described similar IRs and PRs in patients undergoing OD who had an Eth <4 mm, 7–9.9, 10–11.9 and >12 mm. Similarly, others have found no difference in PRs and live birth rates in cycles with an Eth <6 mm compared with those >10 mm (Dain *et al.*, 2013). Moreover, Reis Soares *et al.* (2005) studied the outcomes of >3000 OD cycles using multivariate analysis, which included Eth on the day of OD, and Eth was found not to be related to IR, PRs or miscarriage rates (MRs).

In a systematic review and meta-analysis, Momeni *et al.* (2011) found a significant difference of 0.4 mm in the mean Eth between pregnant and non-pregnant ART patients, which may not be clinically significant. The authors concluded that, although a link between Eth and pregnancy may exist, implantation is probably too complex a factor to be related to Eth.

The mechanism by which a 'thin' endometrium may affect implantation is not known, but it has been related to defective vascularization during the invasive phase. Whereas blood vessel dilatation seems to be necessary in physiological conditions (Steer *et al.*, 1995), and in fact subendometrial blood flow has been associated with Eth (Ng *et al.*, 2006a, b), an endometrium <7 mm leads the embryos closer to the spiral arteries and the higher oxygen concentrations of the basal layer of the endometrium (Casper, 2011), thus affecting IRs (Nikas and Psychoyos, 1997; Oborna *et al.*, 2004). Others have argued that the deleterious effect is mechanical, induced by the catheter during the procedure of embryo transfer (ET), especially in women where the endometrium is too thick (Weissman *et al.*, 1999). Age has also been suggested to be a possible cause of reduced Eth (Amir *et al.*, 2007).

The *endometrial pattern* also appears important. Zhao *et al.* (2012) studied 1933 women undergoing IVF and found that in patients with an Eth <7 mm or >14 mm, IRs and PRs did not differ with respect to the endometrial patterns, whereas in women with an Eth >7 mm to ≤14 mm IRs and PRs were significantly higher in women with a triple-line endometrium than in those with an isoechogenic or hyperechogenic endometrium (35.7 and 55.6% versus 31.9 and 50.2% versus 22.1 and 34.3%, respectively).

The endometrial pattern seems to be the consequence of the serum concentrations of ovarian steroids. A premature increase in Progesterone levels may lead to a premature secretory pattern, which is thought to be damaging to PRs (Zhao *et al.*, 2012). Moreover, Detti *et al.* (2011) observed that ovarian stimulation increased number of the progesterone receptors-B (PR-B), which are normally decreased in the secretory phase (Mylonas *et al.*, 2004), thus creating stimulatory effects and sustaining a proliferative endometrium. Accordingly, the endometrium would be desynchronized with respect to the embryo, leading to implantation failure.

The *endometrial volume* has also been considered. Schild *et al.* (2001) prospectively studied 135 patients undergoing IVF and observed that a minimum endometrial volume of 1.59 ml was needed to achieve a pregnancy. In a prospective study, Yaman *et al.* (2000) reported a minimum volume of 2.5 ml for a favorable pregnancy but concluded that volume on the day of hCG administration did not predict the occurrence of pregnancy.

Concrete cut-off values of ultrasound markers for predicting successful implantation have not been determined. Nevertheless, when a 'thin' endometrium is detected during an ART cycle, physicians have to counsel patients about the possible management options. These include the continuation of the cycle with patients advised about the potentially reduced outcomes, or the cancelation of the cycle with embryo cryopreservation and postponement of the embryo transfer (Check, 2011).

In addition, several adjuvant regimens have been proposed to treat patients with inadequate Eth, including estrogens (Shen *et al.*, 2013), low-dose aspirin (Weckstein *et al.*, 1997; Hsieh *et al.*, 2000; Urman *et al.*, 2000), vaginal sildenafil citrate (Viagra) (Sher and Fisch, 2000, 2002), pentoxifylline (Ledee-Bataille *et al.*, 2002; Letur-Konirsch and Delanian, 2003) and tocopherol (vitamin E) (Ledee-Bataille *et al.*, 2002).

Treating patients with low-dose aspirin might reduce uterine vascular resistance and improve uterine blood flow by shifting local production of thromboxane toward prostacyclin (Weckstein *et al.*, 1997), thereby improving implantation (Wada *et al.*, 1994; Weckstein *et al.*, 1997). However, Check *et al.* (1998) did not find an increase in Eth and uterine blood flow with a low-dose aspirin supplement following frozen embryo transfer. Similar results were observed in prospective and randomized studies by Yao-Yuan *et al.* (2000) in women undergoing intrauterine insemination (IUI), and by Lambers *et al.* (2009) in IVF patients with previous failed conception, in which low-dose aspirin neither improved PRs nor affected the arterial uterine blood flow.

Data are scarce regarding the value of vaginal sildenafil citrate. In a study of only four women, Sher and Fisch (2000) observed that sildenafil citrate might improve endometrial growth and PRs in patients with a thin endometrium. Sher and Fisch (2002) studied 105 women with prior inadequate endometrial development who received sildenafil citrate vaginal suppositories (25 mg, 4 times per day) for 3–10 days. A total of 70% showed an Eth of ≥9 mm with higher IRs and ongoing PRs compared with those who did not respond.

Pentoxifylline (800 mg/day), vitamin E (1000 IU/day) and sildenafil citrate have been used, in isolation or combined, to improve PRs and artery uterine blood flow in women with a thin endometrium, with Eth increasing in ∼70% of cases (Ledee-Bataille et al., 2002; Letur-Konirsch and Delanian, 2003).

In a recent prospective study, Gleicher et al., (2013) administered intrauterine granulocyte colony-stimulating factor (G-CSF) to 21 patients with poor endometrial development (<7 mm) on the day of hCG. On the day of embryo transfer, endometria were 3 mm thicker, regardless of whether they had conceived or not. This study was not controlled, but recently the same group (Barad et al., 2014) published a RCT in which they evaluated the effect of intrauterine G-CSF administration on Eth and clinical PRs. One hundred and forty-one patients were randomized (only six of them had Eth <7 mm), and the authors failed to find any difference between treatment and placebo arms for Eth, PRs and clinical PRs.

Taking into account the variety of controversial data, ultrasonographic evaluation of impaired ER and the subsequent determination of treatment procedure remain challenging issues. There are a lack of RCTs, substantial heterogeneity in the literature, and no established threshold values for either Eth or endometrial volume for favorable PRs and IRs in ART cycles. Moreover, no consensus has been reached on whether the endometrial ultrasound pattern can predict treatment outcome.

## Polyps

Endometrial polyps (EPs) are benign overgrowths of the endometrium with a high incidence rate in women with unexplained infertility (UI) (15.6–32%) (Hatasaka, 2011), endometriosis (36–46.7%) (Kim et al., 2003; Shen et al., 2011) and recurrent miscarriages (15–50%) (Varasteh et al., 1999).

There is evidence that EPs are estrogen-associated lesions (Bergeron, 2002; Taylor et al., 2003) with a prevalence that increases with age (Hatasaka, 2011), as well as with obesity (Onalan et al., 2009).

Although a link between EPs and infertility has been shown in retrospective studies (Foss et al., 1958; Wallach, 1972), the effect of EPs in ART is not clear and is likely underestimated. EPs appear to negatively affect ER and implantation in infertile women, but there is currently a lack of good quality prospective studies evaluating the effects of EPs on IVF.

Due to this lack of data, we currently consider the effects of EPs on spontaneous pregnancy and pregnancy after IUI in order to inform our understanding of the potential role of EPs in IVF.

The literature suggests that polypectomy may be beneficial for patients with UI and EPs. Indeed, four non-randomized studies reported increased spontaneous pregnancy after hysteroscopic polypectomy (Varasteh et al., 1999; Spiewankiewicz et al., 2003; Shokeir et al., 2004; Stamatellos et al., 2008).

In the only RCT involving EPs and reproductive outcomes, Perez-Medina et al. (2005) found PRs of 63.4% in patients undergoing IUI after removal of polyps ($n = 107$) with a mean size of 16 mm, compared with 28.2% in those patients who did not undergo operative hysteroscopy (HSC) ($n = 108$). The authors recommended performing polypectomy in infertile patients with otherwise UI.

The available IVF data are contradictory. Lass et al. (1999) divided patients with EPs <2 cm into two groups: One group (49 women) completed IVF and the other (34 women) cryopreserved and transferred embryos after polypectomy. No difference in PRs was observed, and it was concluded that small polyps have no adverse effect on reproduction. It should be noted that the potential effect of embryo cryopreservation on the success rate was not considered.

In contrast, Batioglu and Kaymak (2005) observed PRs of 50% in patients who underwent polypectomy during an IVF cycle without cycle cancelation, suggesting that, at the very least, this option may not be detrimental to IVF cycle outcome.

Size and location of the polyps have also been addressed, although again in inadequately designed studies. It has been reported that polyps as large as 20–25 mm may not be detrimental to IVF outcome (Lass et al., 1999). Regarding location, it seems that excision of those at the uterotubal junction is associated with significant improvements in PRs (Yanaihara et al., 2008). The mechanism by which EPs may affect fertility in ART is also unclear, but several possibilities have been described (Fig. 1) .

If an EP is detected during an ART cycle, various management options have been reported, including expectant management, cancelation of the cycle and embryo cryopreservation with transfer in a subsequent cycle, and polypectomy without cycle cancelation.

When EPs <10 mm in size are found in symptom-free patients prior to ART, expectant management may be considered, given that spontaneous regression following the menstrual cycle has been observed in 27% of cases. Conversely, EPs ≥15.1 mm are less likely to regress spontaneously (Lieng et al., 2009).

The evidence regarding the effectiveness of polypectomy prior to ART treatment remains insufficient and demands further research (Bosteels et al., 2013). Many clinicians in their daily practice consider excision without electrocautery by HSC appropriate prior to ART, as HSC is a simple, safe and well-tolerated procedure that does not appear detrimental to the IVF cycle outcome irrespective of EP size (Kremer et al., 2000; Guida et al., 2003; Pellicano et al., 2003).

## Intrauterine adhesions and Asherman syndrome

Asherman syndrome (AS) is a condition characterized by complete obliteration of the tubal ostia, uterine cavity and/or the cervical canal with adhesions. Intrauterine adhesions (IUAs) refer to a less severe disorder in which endometrial walls are partially replaced with fibrotic tissue (Panayiotides et al., 2009). Both conditions can cause menstrual irregularities, including amenorrhea, hypomenorrhea or dysmenorrhea, infertility, recurrent pregnancy losses, and disorders of placentation (Yu et al., 2008).

IUAs are usually related to some endometrial iatrogenic trauma, such as dilatation and curettage (D&C) following miscarriage (Friedler et al., 1993), post-partum (Schenker and Margalioth, 1982) or Cesarean section (Badawy et al., 1998); trauma to a non-gravid uterus following

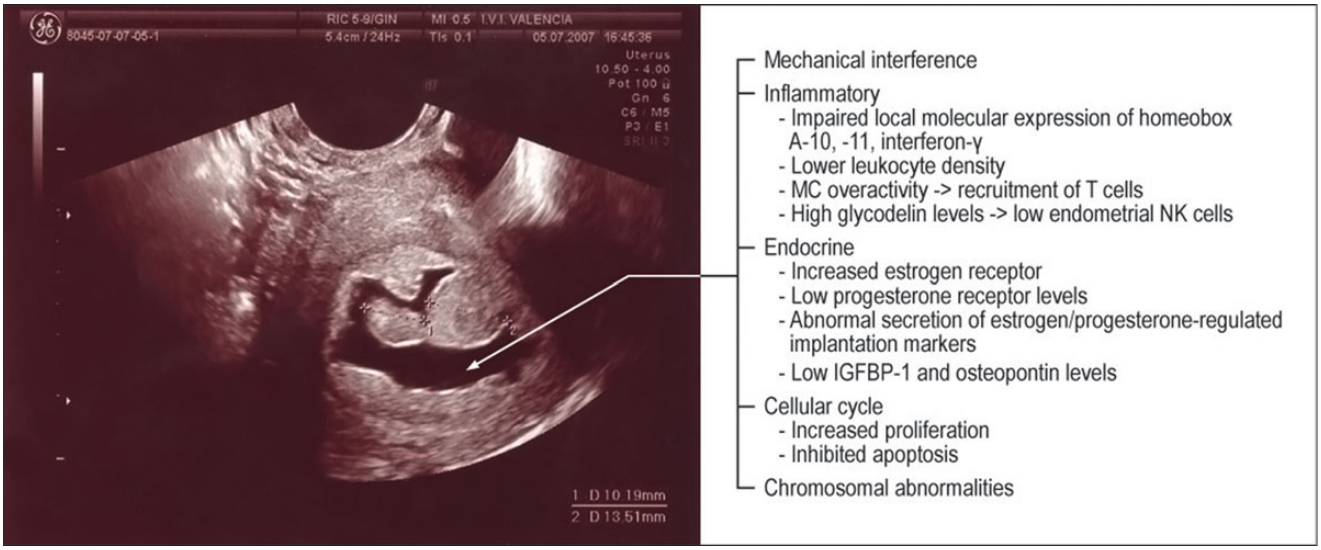


**Figure 1** Proposed mechanisms of action of endometrial polyps (EPs) on implantation. Large EPs interfere mechanically with embryo transport (Bosteels *et al.*, 2010). Fertilization and implantation are affected by immunological factors due to increased mast cell (MC) infiltration and the inflammatory reaction (El-Hamarneh *et al.*, 2013). An increased expression of estrogen receptors and low expression of progesterone receptors is often observed with EPs (Hatasaka, 2011). This may cause an impaired secretion of implantation markers (Mollo *et al.*, 2011; Rackow *et al.*, 2011), insulin-like growth factor-binding protein-1 (IGFBP-1) and osteopontin (Ben-Nagi *et al.*, 2009), as well as glycodelin levels that inhibit natural killer (NK) cell function (Richlin *et al.*, 2002). Moreover, proliferation is increased in the presence of EPs (Vanni *et al.*, 1993). Similarly, apoptosis is inhibited in the polyp glandular epithelium (Taylor *et al.*, 2003; Peng *et al.*, 2009).

HSC (Taskin *et al.*, 2000); endometrial ablation (Taskin *et al.*, 2002; Leung *et al.*, 2003; Mukul and Linn, 2005); infections, in particular *Mycobacterium tuberculosis* (Netter *et al.*, 1956; Bukulmez *et al.*, 1999); and Müllerian duct malformations, particularly septate uterus (Schenker and Margalioth, 1982). In these situations, the basal layer of endometrium and the underlying myometrium may be removed. This induces inflammation, which may not allow regeneration of the lining (Schenker and Margalioth, 1982; Schenker, 1996), thus causing adherence of the apposed myometrial surfaces and the formation of dense fibrous adhesions (Lo *et al.*, 2008). This may explain the lack of regeneration of the endometrial functional layer in AS and IUAs (Lo *et al.*, 2008; Panayiotides *et al.*, 2009).

In ART patients, IUAs have been described in as many as 16% of women undergoing HSC before their first cycle (de Sa Rosa e de Silva *et al.*, 2005). However, this incidence is highly dependent on the woman's previous obstetric background, for example, the number of pregnancies followed by D&C or uterine surgery (Hooker *et al.*, 2014). Patients with three or more miscarriages have been shown to have a significantly higher incidence of IUAs (OR 2.1, 95% CI: 1.09–4.1) than women with only one miscarriage (Hooker *et al.*, 2014).

AS appears to affect fertility and reproductive outcomes, depending especially on the degree and severity of the adhesions, as well as their recurrence and menstrual pattern after adhesiolysis. Consistent data on the link between IUAs and reproductive outcomes after ART are lacking. Because of this, we analyze the effects of IUAs on spontaneous pregnancy.

Schenker and Margalioth (1982) found infertility in two-thirds of patients with AS. They observed pregnancies in 45% of women with IUAs who did not receive treatment, 40% of whom had spontaneous abortion and 23% with preterm deliveries. Others studies found live birth rates ranging from 18.3% before surgery to 68.6% after adhesiolysis (Acunzo *et al.*, 2003). The worst clinical outcomes have been associated with more severe adhesions (Roy *et al.*, 2010). Thus, although spontaneous pregnancy is possible with severe IUAs, IUAs do affect fertility to some extent, and therefore should be taken into account before attempting ART.

Although studies analyzing how AS affects reproductive outcome are lacking, IUAs are thought to impair ER by reducing PRs and increasing the risk of miscarriage (Schenker and Margalioth, 1982; Schenker, 1996).

The best way to treat IUAs is to prevent their formation by reducing the number of D&C procedures. Indeed, in a recent systematic review and meta-analysis of IUAs (Hooker *et al.*, 2014), conservative and medical treatments of miscarriage have been proposed as a valid alternative to surgical management of miscarriage. However, if IUAs are present in any form or severity, the first-line treatment should be HSC adhesiolysis with hysteroscopic scissors to avoid thermal endometrial damage related to electrosurgery (Duffy *et al.*, 1992; Roge *et al.*, 1997) that aims to repair the impaired lining, restoring normal uterine cavity and fertility.

In fact, adhesiolysis allows the endometrium to restore its anatomy and function, depending on the extent of the adhesions and the preoperative appearance of the endometrium observed with TVS (Schlaff and Hurst, 1995). Much more than other conditions, IUAs are associated with a high recurrence rate (3.1–62.5%), which is dependent on the severity of adhesions.

When adhesiolysis or other surgical interventions are performed in the endometrial cavity, several surgical and pharmacological post-operative measures have been used to keep separate the opposing

uterine sides and to prevent the reformation of IUAs. These procedures have been shown to improve reproductive outcomes after adhesiolysis. Surgical techniques include the insertion of an intrauterine device (IUD) (Lin et al., 2013), a Foley catheter balloon (Amer et al., 2005; Lin et al., 2013), or the intrauterine application of modified hyaluronic acid (HA) (Acunzo et al., 2003; Lin et al., 2013), HA (ACP) gel (Hyalobarrier gel; Baxter, Pisa, Italy) (Pabuccu et al., 1997), and polyethylene oxide-sodium carboxymethylcellulose gel (Di Spiezio et al., 2011; Fuchs et al., 2014).

Other interventions, such as antibiotics (Knopman and Copperman, 2007), the use of IUDs containing estrogens/cytokines (Tu et al., 2013) or the use of stem cells (Cervelló et al., 2013), currently lack the evidence required to support their use in clinical routine.

## Fibroids

Uterine fibroids (leiomyomas) are benign tumors that arise from the myometrium. They are formed of disorganized smooth-muscle cells surrounded by an extracellular matrix which accounts for tumor expansion. They cannot only be present as isolated tumors of varying sizes, but also as multiple small tumors disseminated among the entire myometrial layer. Fibroids can be submucosal, intramural or subserosal in location. Both location and size determine their symptomatology.

The exact prevalence of fibroids in the infertile population is unknown, although it is estimated to be around 8% in women aged 33–40 years (Borgfeldt and Andolf, 2000). This is higher than expected due to the influence of age at childbearing. In fact, a study including IVF/ICSI patients showed an incidence of 26.7% (Hart et al., 2001).

It is generally accepted that subserosal leiomyomas do not affect gestation (Pritts et al., 2009). On the other hand, submucosal and intramural leiomyomas, which protrude into the endometrial cavity, are associated with poorer outcomes which can be overcome by myomectomy (Hart et al., 2001; Surrey et al., 2005; Somigliana et al., 2007; Pritts et al., 2009).

The reproductive impact on ART of intramural fibroids that do not affect the endometrial cavity is more controversial, as size, number and location all must be considered. Different inclusion criteria and methodological approaches have made the comparison of different studies difficult. Sunkara et al. (2010) published the most comprehensive systematic review and meta-analysis on this topic, including 6087 patients, with a series of straightforward messages. Pooling the results from 11 studies, they observed a statistically significant 21% relative reduction in live birth rates for women with non-cavity-distorting intramural fibroids compared with women without fibroids (relative risk (RR) 0.79, 95% confidence interval (CI): 0.70– 0.88). When only studies with a prospective design were considered (Check et al., 2002; Khalaf et al., 2006), the reduction in live birth rates was as high as 40% (RR 0.60, 95% CI: 0.41–0.87) (Sunkara et al., 2010).

Two large studies have been published since this meta-analysis. Somigliana et al. (2011) studied 119 women with asymptomatic intramural or subserosal fibroids <5 cm and compared these outcomes with 119 controls: The live birth rates were similar (18 versus 13%, respectively), and the adjusted odds ratio (OR) was 1.45 (95% CI: 0.71–2.94). It was concluded that the presence of asymptomatic small fibroids did not affect ART outcomes.

Yan et al. (2014) included 249 women undergoing their first IVF/ICSI cycle with different types of fibroids and compared them with 249 controls without fibroids. After matching for several variables, delivery rates were 33.7 and 30.5% for controls and women with fibroids, respectively (adjusted OR 1.03 (95% CI: 0.95–1.11)). A significant negative effect on delivery rate was noted when the largest tumor diameter was >2.85 cm.

Another reason to treat fibroids before attempting pregnancy is their potential for growth during gestation. A prospective study of 42 women showed that fibroid volume increased >10% during pregnancy. This growth was independent of fibroid size, location and maternal age (De Vivo et al., 2011). These findings are in accordance with a positive hormonal influence upon tumors (Bulun, 2013).

Regardless of their size or location, intramural fibroids may have paracrine molecular effects on the adjacent endometrium, causing excessive uterine bleeding or defective implantation. The negative influence on ART outcomes when non-cavity-distorting intramural fibroids are present may be explained by altered uterine vascular perfusion and/or impaired ER. In this context, Arslan et al. (2005) analyzed the expression profiles of 22 283 genes in paired samples of leiomyoma and adjacent normal myometrium. They found a series of genes that were up- and down-regulated in fibroids compared with adjacent tissue. One of the altered genes was transforming growth factor (TGF)-β3. The TGF-β pathway is a key regulator of cellular growth and differentiation (Luo et al., 2003), but none of the pathways related to implantation were altered.

Horcajadas et al. (2008) specifically looked at genes related to the window of implantation (WOI) which were described previously (Horcajadas et al., 2007). A total of 22 endometrial samples were collected from women with single intramural leiomyomas of different sizes not encroaching the endometrium. Healthy fertile normal-cycling women served as the control group and all the samples were collected 7 days after the LH peak. There was a strong positive and negative correlation in the expression profile of 69 genes according to leiomyoma size, but only 3 of the 25 genes related to the WOI were dysregulated (Horcajadas et al., 2008).

Because uterine fibroids might have an impact on conception, different treatment options exist. The initial approach before ART is myomectomy, with the rate of new fibroid appearance within 3 years being 5% (Candiani et al., 1991).

Additionally, some other points need to be addressed. First, younger age might be a specific indication for myomectomy. In fact, women <37 years with uterine fibroids have shown a significant 25% relative reduction in live birth rate (RR 0.75, 95%; CI: 0.62–0.89) (Sunkara et al., 2010).

Second, not many studies have addressed the relation between leiomyoma size and ART outcomes. Oliveira et al. (2004) showed that women with fibroids ≥4 cm had significantly lower delivery rates than women with smaller tumors. Similarly, Bulletti et al. (2004) showed a benefit in removing fibroids of 5 cm in size. The outcomes with fibroids ≤5 cm are less clear. Some studies reported that fibroids significantly reduced ongoing PRs by 64% in first IVF cycles (Hart et al., 2001), and cumulative PRs by 40% after three attempts over a 12-month period (Khalaf et al., 2006). Others have compared matched cohorts of women without fibroids and women with fibroids ≤5 cm and found no difference in live births, with an adjusted OR of 1.45 (95% CI: 0.71–2.94) (Somigliana et al., 2011).

Third, the route of myomectomy is also a matter of debate. The use of laparoscopy appears advantageous for post-operative recovery and morbidity, but there is no clear benefit for the laparoscopic approach with respect to live birth outcomes (Metwally et al., 2012).

Our current practice is therefore to perform a laparoscopy for those fibroids classified by The International Federation of Gynecology and

Obstetrics (FIGO) as stages 3–6, provided they have a size (≥4 cm) that can be easily identified and removed by laparoscopy (Munro *et al.*, 2011) (Fig. 2). Smaller fibroids might also be considered for surgery if there are previous failed ART attempts, but only when it is feasible with a low probability of complications. If the endometrial cavity is not reached during myomectomy, ART can proceed 3 months after surgery. In cases where the endometrium is visualized, we recommend a uterine healing of 6 months.

More recently, semi-invasive approaches employing imaging and medical therapies have been introduced and could be used if surgery is contraindicated. These approaches have been shown to decrease tumor size and volume for a period of time; however, the tumor does not disappear entirely, and these methods have not been shown to improve the reproductive outcomes of ART.

GnRH agonists (GnRHa) induce a significant and rapid reduction in fibroid size (35–65%), but cannot be administered for >3–6 months (Stewart, 2001). Mifepristone, an active antiprogestin, has been shown to decrease fibroid size from 26 to 74% with oral doses ranging from 5 to 50 mg for 6 months (Steinauer *et al.*, 2004; Fiscella *et al.*, 2006) (Fig. 2). The vaginal route is also effective within 3 months (Yerushalmi *et al.*, 2014). The induction of endometrial hyperplasia is another potential risk that should be taken into consideration.

The selective progesterone receptor inhibitor ulipristal acetate has proved to be effective in the treatment of symptomatic fibroids (Donnez *et al.*, 2012a, b) (Fig. 2). GnRHa appear to be more effective than ulipristal acetate, resulting in a greater reduction in fibroid volume. On the other hand, ulipristal acetate provides a more prolonged volume reduction after treatment is discontinued compared with the rapid regrowth observed in GnRHa treatments (Donnez *et al.*, 2012b). Endometrial changes, which disappear after 6 months, might also be an issue with this medication.

There are other medical options, such as danazol, the selective estrogen receptor modulator raloxifene, and aromatase inhibitors (Olive *et al.*, 2004; Bulun *et al.*, 2005; Ohara, 2005; Somigliana *et al.*, 2007; Ke *et al.*, 2009). However, their value is questionable given the lack of data on the potential benefits on PRs after suspension of treatment.

Other semi-invasive alternatives for the reduction of tumor size and volume include uterine artery embolization (UAE), laparoscopic myolisis and magnetic resonance imaging (MRI) guided focused ultrasound (MRgFUS). One study found that employing UAE decreased uterine

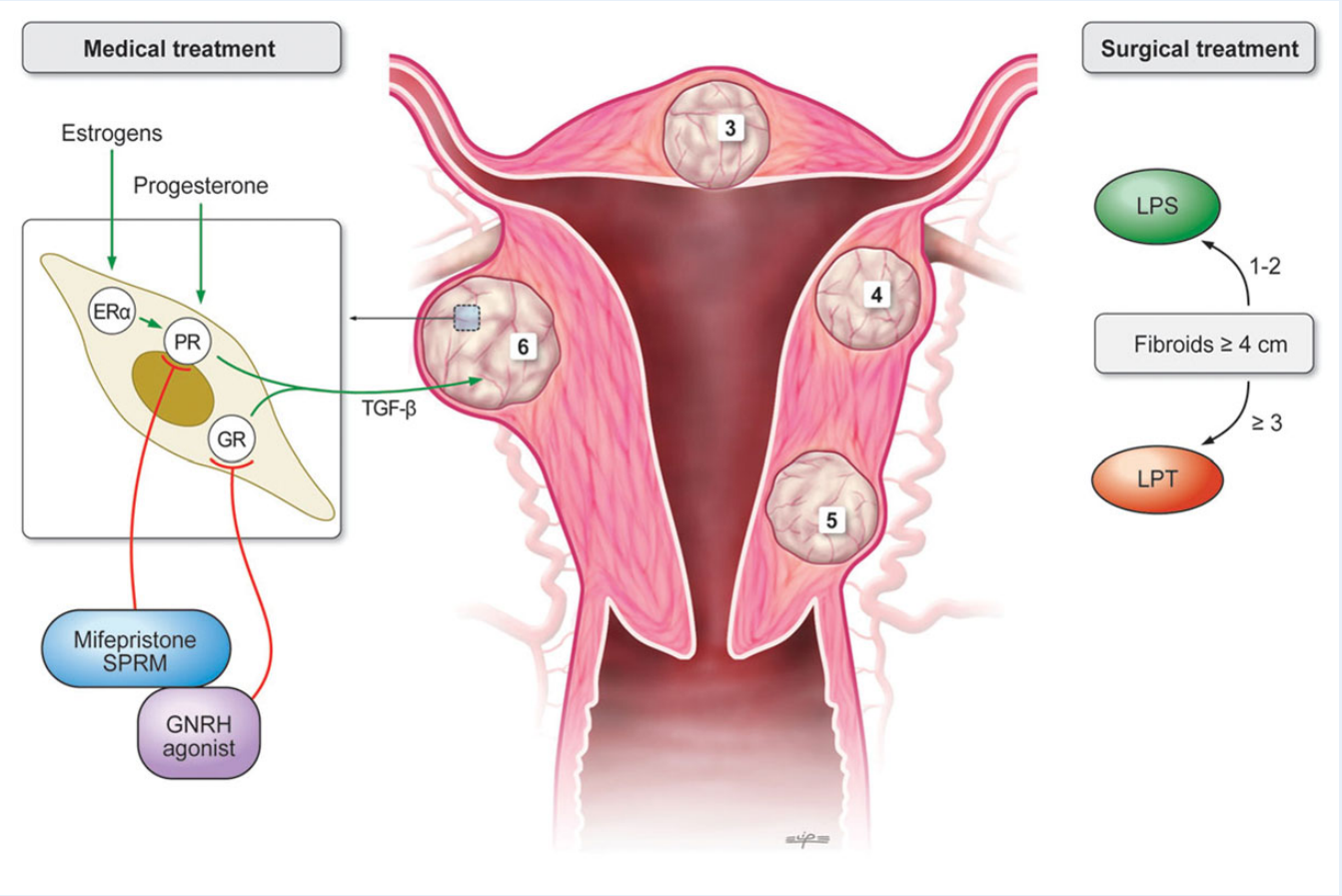


**Figure 2** Treatment of uterine intramural fibroids before attempting assisted reproduction technology (ART). Although the evidence is not strong, there is a common trend to remove fibroids ≥4 cm if they protrude on the serosal surface. Only stages 3–6 of the FIGO classification can fit these requirements (Munro *et al.*, 2011). Whether laparoscopy (LPS) or laparotomy is performed depends on the total number of fibroids and the surgeon's skills, but LPS is initially recommended. New medical therapies that target estrogen receptor alpha (ER-α), progesterone (PR) or GnRH (GR) receptors and block the transforming growth factor (TGF)-β pathway may provide a non-invasive approach to reduce size and increase ART outcomes in the future. SPRM, selective progesterone receptor modulator.

volume ~50% (Gupta et al., 2012). Only a few studies, however, have addressed fertility after UAE and their quality is poor. UAE has been classically contraindicated in patients desiring to preserve their fertility. Initial reports showed transient or permanent amenorrhea, with other symptoms of ovarian failure appearing in up to 5% of women (Chrisman et al., 2000; Walker and Pelage, 2002). Moreover, another study demonstrated that UAE was associated with less pregnancies and more miscarriages than myomectomy (live birth: OR 0.33, 95% CI 0.11–1.00; pregnancy: OR 0.29, 95% CI 0.10–0.85) (Mara et al., 2006). Redecha et al. (2013) prospectively followed 98 women undergoing UAE, 21 of whom desired to become pregnant and the PR in this subgroup was 23.1%. Recently, Torre et al. (2014) treated 66 women with extensive symptomatic fibroids with UAE who were prospectively followed for nearly 3 years, and 31 of whom were actively seeking pregnancy. Only 1 of these 31 achieved pregnancy (monthly fecundability rate 0.1%; 95% CI 0–0.3%).

MRgFUS is a method of thermal ablation for treating leiomyomas (Stewart et al., 2003). The reduction of a fibroid's volume after 6 months is moderate (13.5%) (Stewart et al., 2006). Using GnRHa 3-month pretreatment to reduce fibroid vascularity has been shown to reduce total volume by 21% (Smart et al., 2006). Very little information is available with regard to ART treatments, most of which are published as case reports (Zaher et al., 2011).

Another method of thermal ablation is radio-frequency myolisis using laparoscopically-guided bipolar electric probes. Initial studies showed a decrease in fibroid volume of up to 50% in the first 6 months (Bergamini et al., 2005; Ghezzi et al., 2007). No reports are available for ART patients.

## Adenomyosis

Adenomyosis uteri is characterized by the presence of ectopic endometrial glands as a *diffuse adenomyosis* involving the myometrium, or localized as an *adenomyoma* resembling a fibroid. It is a common disorder in the fourth and fifth decades of life (Ferenczy, 1998). The exact prevalence of adenomyosis in an infertile population is not known (Maheshwari et al., 2012), but older age and the association with endometriosis in 27–79% of cases contribute to its increased presence in ART centers (Kunz et al., 2005; Larsen et al., 2011).

A recent meta-analysis by Vercellini et al. (2014) addressed the impact of adenomyosis on ART. They first showed the important heterogeneity and asymmetry among nine selected studies, both prospective and retrospective. None of them had live birth rates as primary outcome, but rather focused on clinical pregnancy and miscarriage rates. Their analysis showed that clinical PRs seem to be affected by the presence of adenomyosis (40.5 versus 49.8% in controls) in IVF/ICSI (RR of 0.71, 95% CI, 0.51–0.98; $I^2 = 78.1\%$, $P = 0.010$), but not in OD (RR 0.90, 95% CI, 0.75–1.08). Miscarriage was observed in 31.9% of women with adenomyosis compared with 14.1% in controls. The RR for miscarriage ranged from 0.57 (95% CI, 0.15– 2.17) to 18.00 (95% CI, 4.08–79.47) ($I^2 = 67.7\%$, $P = 0.005$).

Thus, although it appears that adenomyosis may have a negative impact on ART outcomes, the available literature suffers from several flaws, including a lack of RCTs (most are retrospective); treatment with long acting GnRH analogs (an established treatment of adenomyosis); inconsistent diagnosis criteria (with endometriosis sometimes included); and small sample sizes, with 95% CIs far too wide in some studies (Mijatovic et al., 2010; Costello et al., 2011; Martínez-Conejero et al., 2011; Youm et al., 2011; Salim et al., 2012; Thalluri and Tremellen, 2012).

The mechanism by which adenomyosis might affect ART is also not known. Experimental work has shown some potential mechanisms that may explain a possible deleterious effect on the implantation process. A number of proteins and growth factors related to the process of implantation have been shown to be altered in women with adenomyosis. These include matrix metalloproteinases (MMP) 2 and 9 (Bruner et al., 1997), E-cadherin (Ota and Tanaka, 1997) and leukemia inhibitory factor (LIF) (Xiao et al., 2010).

Several inflammatory cytokines, such as interleukin (IL)-1, IL-6, IL-8 and IL-10, have been shown to be elevated in women with adenomyosis. Similarly, vascular endothelial growth factor (VEGF) expression is altered, thus affecting endometrial angiogenesis (Li et al., 2006).

Glutathione peroxidase, xanthine oxydase, cyclooxygenase-2 (COX-2), superoxide dismutase and catalase expression were found to be persistently and aberrantly high in the endometria of women with adenomyosis (Ota et al., 1999, 2000, 2001a, b, 2002). Excessive oxidative stress and the production of nitric oxide (NO) and peroxynitrite are known to create tissue damage and could also affect implantation (Chwalisz et al., 1999; Purcell et al., 1999).

HOXA10 gene expression is also significantly reduced in adenomyosis, which in turn could explain a diminished implantation (Fischer et al., 2011). We investigated the gene expression profile during the WOI in six women with MRI- and ultrasound-proven adenomyosis and six controls, and found no difference in gene expression between groups (Martínez-Conejero et al., 2011).

Successful establishment and maintenance of pregnancy requires decidualization. RCAS1 is one protein involved in the local immune reaction to pregnancy. It is responsible for the activation of NK cells and T lymphocytes, being differentially expressed in women with adenomyosis (Wicherek, 2009).

The literature on the treatment of adenomyosis before ART consists primarily of case reports and short series, making any recommendation based on evidence difficult. The most widely employed approach has been the use of depot GnRHa for 3–6 months, alone, or in combination with cytoreductive surgery.

GnRHa may lead to regression of lesions through the hypogonadotropic status induced in an estrogen-dependent disease such as adenomyosis (Huang et al., 1999). Moreover, as illustrated in Fig. 3, GnRHa may provide potential mechanisms of direct action on adenomyotic lesions through its type I and II receptors, which are present in the endometrium (Raga et al., 1998; Cheon et al., 2001; Millar, 2003).

However, the clinical evidence that GnRHa might improve fertility in women with adenomyosis is scarce. Only case report series can be found, some showing a 50% reduction in uterine size and/or volume after 3–6 months of therapy (Nelson and Corson, 1993; Huang et al., 1999).

Danazol provides regression of lesions by inducing hypoestrogenism after central suppression and a direct action, which leads to reduced cytochrome P450 expression (Ishihara et al., 2003), endometrial cell proliferation (Braun et al., 1994) and increasing apoptosis in endometrial cells (Ueki et al., 2004). In one study, Danazol was given orally at a daily dose of 400 mg/day during 1 month, or locally as a vaginal ring in 35 women, 13 of whom reached pregnancy (Igarashi, 1990).

The levonorgestrel-releasing IUD has been used in 25 women with menorrhagia associated with adenomyosis (Fedele et al., 1997). After

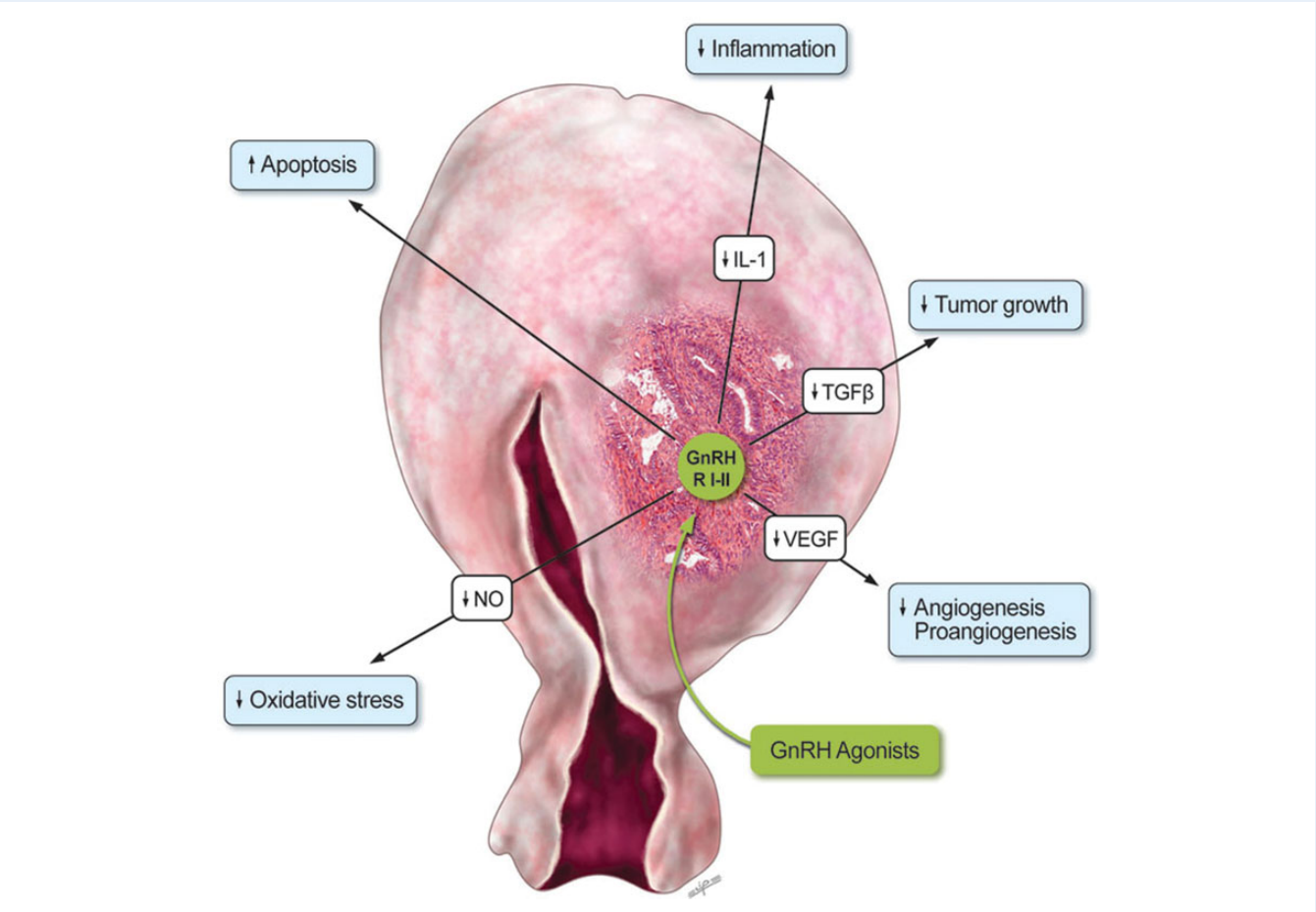


**Figure 3** Potential mechanism of direct action of GnRHa on adenomyotic lesions. GnRH agonist (GnRHa) decreases leading to an overexpression of aromatase cytochrome P450 (Kitawaki *et al*., 1997, 1999; Ishihara *et al*., 2003). Decreased enzymes involved in the synthesis of reactive oxygen species induce nitric oxide (NO) overexpression and oxidative stress through the generation of peroxynitrite (Ota *et al*., 1999, 2000, 2001a, b, 2002). GnRHa enhances the apoptosis index (Raga *et al*., 1998; Wang *et al*., 2002; Meresman *et al*., 2003; Ueki *et al*., 2004; Bilotas *et al*., 2007) and decreases the secretion of interleukin (IL)-1 and VEGF (Wu *et al*., 2009). GnRHa reduces the inflammatory reaction and suppresses cellular proliferation in adenomyotic tissue (Khan *et al*., 2010a, b). GnRHa induces the expression of the inhibitory Smad7, with a potential interruption of TGF-β receptor signaling mediated in the endometrium (Luo *et al*., 2003).

12 months of treatment, 15 patients improved and 16 had regular menses. The uterine volume also decreased. Similar results have been published by others (Sheng *et al*., 2009).

Surgery for the treatment of adenomyosis, or a combination of surgery and GnRHa, has been extensively documented in case reports and short series, but no data on specific outcomes in ART are available. The surgical techniques were recently reviewed systematically (Grimbizis *et al*., 2014). Conservative surgery reduces hypertrophy and subsequently improves function by bringing the uterine layers closer together (Tadjerouni *et al*., 1995). It also enhances blood supply, thereby facilitating GnRHa action (Wang *et al*., 2000). However, the number of cases that are converted to hysterectomy due to unexpected surgical complications has not been reported. Furthermore, the removal of adenomyotic tissue is often accompanied by excision of healthy myometrium, which is associated with a high risk of uterine rupture during pregnancy (Wang *et al*., 2006).

With respect to pregnancy outcomes with GnRHa, Wang *et al*. (2009) retrospectively studied two groups of women. In the first group, adenomyotic tissue was surgically removed and GnRHa was given for 6 months ($n = 28$). A second group ($n = 37$) only received 6 months of GnRHa. They noted uterine regrowth after the effect of GnRHa had disappeared in the GnRHa-only group. Cumulative spontaneous PRs after 36 months were significantly higher with the combined treatment of surgery plus GnRHa.

Other semi-invasive approaches can be attempted for the treatment of adenomyosis. Kim *et al*. (2004) employed polyvinyl alcohol particles sized 250–710 mm to perform UAE in 43 patients and reported a volume reduction of 32.5%. Rabinovici *et al*. (2006) have employed MRgFUS to treat a patient with focal adenomyosis. The tumor size was reduced by 50% and the patient conceived spontaneously. No report has addressed the use of these two approaches in ART.

## Hyperperistaltism

Uterine peristaltic waves originate in the subendothelial myometrium and are estrogen and progesterone-dependent. They reach a pre-

ovulatory peak of cervico-fundal movements that are believed to actively transport sperm from the vagina into the oviduct (Ijland et al., 1996; Kunz et al., 1996), characteristic of the periovulatory period. After ovulation, wave activity decreases to provide an adequate environment for implantation (Ijland et al., 1997a, b; Fanchin and Ayoubi, 2009). In cycles with conception, uterine contractions decrease (Ijland et al., 1997b). If peristaltic activity is excessive in the luteal phase, the embryo may miss the implantation site.

The action of estrogens on uterine contraction is likely mediated by the stimulation of locally synthesized oxytocin, and to a lesser extent vasopressin, acting via oxytocin and V1A subtype receptors (Chibbar et al., 1995; Akerlund et al., 1999). PGF2a synthesis is also stimulated by estrogen action (Flint et al., 1986).

In ART, increased uterine peristalsis has long been recognized as a possible cause of implantation failure (Fanchin et al., 1998). Using mock embryo transfer, some authors have estimated it to be as high as 50–60% (Knutzen et al., 1992; Mansour et al., 1994), while other estimates are around 15% (Poindexter et al., 1986; Zhu et al., 2014).

Fanchin et al. (1998) measured uterine contraction frequency immediately prior to embryo transfer and its effect on outcomes in 209 women. Patients were divided according to uterine contraction frequency, from $\leq$3 to >5.0 contractions/min. Significant stepwise decreases were observed in clinical PRs (53–14%), ongoing PRs (36–11%) and IRs (21–4%), suggesting mechanical rejection of the embryos from the endometrial cavity. This notion is further supported by an RCT with atosiban, described below.

Moreover, Bulletti et al. (2002) found increased uterine contractions in a 10-min period in women with endometriosis compared with controls. Yoshino et al. (2010) studied women with fibroids and found that those who were considered to have low-frequency uterine contractions had a 34% pregnancy rate, while for patients with high-frequency contractions the pregnancy rate was 0%. Fibroids contain similar oxytocin and vasopressin receptors as normal myometrium (Fuchs et al., 1998).

Zhu et al. (2012) studied uterine peristaltic activity in the same woman in different moments of a natural and a stimulated cycle. They confirmed a significant increase in wave frequency at ovulation and 2 days later in stimulated compared with natural cycles, but there was no correlation with the 10-fold increase in serum estradiol levels observed after controlled ovarian hyperstimulation (COH) (Ijland et al., 1998; Zhu et al., 2012). Moreover, most waves moved in a cervico-fundal direction (CF, 70–90%), with few being fundal-cervical (FC, 5–20%). However, 2 days after ovulation the CF/FC ratio was higher in the COH cycles, showing an apparent protective effect of COH against embryo rejection (Zhu et al., 2012).

To avoid a detrimental effect of hyperperistaltism, a gentle embryo replacement is mandatory. In fact, the use of a tenaculum increases serum oxytocin levels (Dorn et al., 1999). Recently Zhu et al. (2014) showed that uterine peristalsis exerts control over embryo migration and could adversely affect the chances of pregnancy if the wave frequency is too high. An embryo transfer procedure did significantly increase uterine peristalsis, however, at the end of the recording period 84% of the cases maintained the dye in the endometrial cavity. Removal of cervical mucus and the use of soft catheters were associated with a decreased ejection of blue dye (Mansour et al., 1994).

Other studies, however, have not found an increased incidence of peristaltic waves during the transfer procedure (van Gestel et al., 2009; Torre et al., 2010). These contradictory results might be explained by the way investigators manipulated the uterus.

Mansour (2005) performed an RCT in which patients ($n$ = 325) were randomized to have the screws of the vaginal speculum loosened, which thereby exerted a gentle pressure on the cervical portio vaginalis for a few minutes prior to ejecting the embryos, or to a control condition with no intervention ($n$ = 314): Clinical PRs (67 versus 47.8%; OR 1.39; 95% CI 1.11–1.74, respectively) and IRs (33.3 versus 21.5%; OR 1.54; 95% CI 1.26–1.89, respectively) were both significantly improved in the intervention group (Mansour, 2005).

Another strategy is to replace blastocysts, as peristalsis decreases 7 days after ovulation in both natural (Ijland et al., 1996) and ART cycles (Fanchin et al., 2001b; Ayoubi et al., 2003). However, no clinical trial has been published evaluating the effectiveness of this procedure.

Fanchin et al. (2001a) randomly allocated patients to receive one of two regimes of vaginal progesterone, one group starting immediately after oocyte retrieval, and the other 2 days after retrieval. A significant decline in uterine contractions at the time of embryo transfer was observed when starting immediately after oocyte retrieval, with a trend toward higher PRs and IRs.

Moraloglu et al. (2010) targeted the myometrial oxytocin and vasopressin receptors with the mixed oxytocin/vasopressin V1a antagonist, atosiban. In a randomized placebo-controlled study with 180 women, patients in the treatment group received intravenous atosiban 30 min before embryo transfer with a bolus dose of 6.75 mg, and the infusion was continued at a rate of 18 mg/h. After embryo replacement, the dose was reduced to 6 mg/h and the infusion was continued for 2 h (total administered dose: 37.5 mg). Significant increases in clinical PRs and IRs, and a significant decrease in MRs, were observed for the treatment group versus control.

Pinheiro et al. (2003) employed terbutaline and ritodrine, which are β-mimetic agents, to improve implantation. Ninety women received 10 mg of terbutaline daily for 15 days starting on the day of oocyte retrieval. A second group of 90 patients received 20 mg of ritodrine daily during the same period of time. An additional 45 women served as controls. Similar IRs and ongoing PRs were observed between groups.

Non-steroidal anti-inflammatory drugs have also been employed. Moon et al. (2004) randomized 188 patients to Piroxicam or placebo, and observed significantly improved IRs, from 8.6 to 18.7%. Kido et al. (2009) reported three cases with documented uterine peristalsis that were treated with the anticholinergic drug hyoscine bromide at the time of embryo transfer, all of whom delivered babies.

## Size and shape of the uterus

The uterus develops embryologically from the fusion of the paramesonephric (Müllerian) ducts in the midline about the 10th week of pregnancy. Müllerian anomalies have been related to major disturbances in development (agenesis, hypoplasia, unicornuate uterus), fusion of the ducts (uterus didelphys, bicornuate uterus) and resorption failure of the midline uterine septum (septate uterus, arcuate uterus) (Grimbizis et al., 2001; Hassan et al., 2010). These anomalies are often associated with urinary tract and skeletal malformations. Their origin is unknown, although they have been associated with mutations in some genes.

The prevalence of these anomalies varies widely throughout the literature according to the classification system employed, the method used for diagnosis, and whether general, infertile, or recurrent miscarriage

populations have been analyzed. Taking into account the most accurate diagnostic tools and the American Fertility Society classification system (AFS, 1988), in which most of the current information about Müllerian malformations is based, their prevalence has been estimated at 7–8% in the infertile population, with different incidences according to the type of defect: Absence of development 0.4–0.6%; abnormal fusion 0.2–0.3% for didelphys, and 0.8–1.1% for bicornuate uterus; absence of resorption 3.0–3.9% for septate, and 1.8–2.1% for arcuate uterus. The prevalence of all types of these defects in the general fertile population is 5.0–6.7% (Saravelos *et al.*, 2008; Chan *et al.*, 2011a).

## Absence of development

The *hypoplastic uterus* is characteristic of women with *Turner syndrome* (Khastgir *et al.*, 1997; Abir *et al.*, 2001; Hovatta, 2012). Spontaneous pregnancies have been described in only 2–10% of affected women (Hadnott *et al.*, 2011; Hovatta, 2012). Most pregnancies are achieved by OD, although some occur with IVF when oocytes are still present or when cryopreservation of oocytes or ovarian tissue has been performed at younger ages (Karnis, 2012; Hovatta, 2012). Women with Turner syndrome present increased risks of hypertensive disorders (30%), aortic dissection (2% mortality), and thyroid disease during pregnancy and up to one year after delivery (Chevalier *et al.*, 2011; Hagman *et al.*, 2013a). However, neonatal outcomes are generally reassuring, with a preterm birth rate of 8% and a low birthweight rate of 8.8% in singletons after OD (Hagman *et al.*, 2013b). IRs and PRs are also similar to those found in other oocyte recipients, but the risk of miscarriage is increased (40–60%) (Khastgir *et al.*, 1997; Abir *et al.*, 2001).

*Swyer syndrome* (XY gonadal dysgenesis or 46,XY pure gonadal dysgenesis) is an infrequent condition associated with mutations in the sex determining region of the Y chromosome gene or with other testis-determining factors. It is characterized by the presence of a hypoplastic uterus. Recently, Creatsas *et al.* (2011) published a case-report and reviewed 12 other publications on this syndrome with a total of 16 patients who became pregnant with OD. In seven of these cases, pregnancies were double or triple, and four cases presented gestational hypertension or pre-eclampsia. With hormonal therapy the uterine size was increased to almost normal dimensions. In these cases, single embryo transfer (SET) is recommended, not only because of the uterine size, but also because of the potential medical complications associated with Turner or Swyer syndromes (Hagman *et al.*, 2013b).

Congenital vaginal and uterus agenesis occurs in some disorders, such as *Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome* and androgen insensitivity syndrome with 46,XY karyotype. MRKH syndrome is more frequent and refers to the congenital absence of the vagina with associated variable uterine development resulting from Müllerian agenesis or hypoplasia. This syndrome affects between 1:4000 and 1:10000 female live births. The uterus and cervix are often absent, but 7–10% of such women have a rudimentary uterus with functional endometrium, and up to 25% have cavitated Müllerian remants (Reichman and Laufer, 2010a, b).

A successful pregnancy after zygote intrafallopian transfer (ZIFT) has been described in a specific phenotype in which cervical atresia is associated with a normal midline uterus and a normally formed vaginal vault (Thijssen *et al.*, 1990). A transabdominal cerclage was placed at 14 weeks of pregnancy, and an elective lower segment Cesarean section was carried out for delivery.

Most patients with uterine agenesis present at least one normal ovary. ART is performed through surrogates after COH in order to have a genetically related progeny, since the congenital absence of vagina and uterus is not commonly transmitted to offspring (Petrozza *et al.*, 1997; Ravel *et al.*, 2009). Pregnancy and live birth rates with the patient's own gametes in surrogate mothers are generally quite high, with a reported PR of 42.9% and take-home baby rate of 21.4% per embryo transfer (Beski *et al.*, 2000).

In women with the typical MRKH form (isolated uterovaginal aplasia/hypoplasia), the need for gonadotrophins is lower and the duration of ovarian stimulation is shorter than in women with the atypical form (the addition of malformations in the ovary or renal system). Similarly, the mean number of follicles, metaphase II oocytes and cleaving embryos obtained seems to be higher among women with the typical form. However, fertilization rates, cleaving embryo rates, mean number of transferred embryos, embryo quality and PRs in surrogate mothers are similar (Raziel *et al.*, 2012).

Transvaginal oocyte retrieval can be technically difficult or impossible due either to the lack of vaginal elasticity in surgically reconstructed vaginas, or to the presence of ectopically located gonads sometimes found by imaging techniques in the upper abdomen, in the pelvic brim, or within the inguinal canal. In some of these cases, laparoscopic or transabdominal recovery is needed (Wood *et al.*, 1999; Reichman and Laufer, 2010b). Uterine transplantation is another promising option for non-functioning or non-existing uterus. However, to date no live birth has been described in humans following this procedure (Brännström *et al.*, 2014).

The *unicornuate uterus* has been classically related to pregnancy complications, but not so clearly to impaired fertility. In addition, data from women requiring ART are scarce. In one study (Lavergne *et al.*, 1996), IRs and PRs per transfer were lower after IVF in women with unicornuated, pseudo-unicornuated or bicornuated uteri compared with IVF controls with a normal uterus.

Patient prognosis is extracted from the published experience with natural conception. A meta-analysis including nine studies and 3805 women showed that conception rates were not significantly different in women with unicornuate compared with normal uterus (Chan *et al.*, 2011b). In another review, however, pregnancy complication rates were quite high, including 24.3% first trimester miscarriage, 9.7% second trimester miscarriage, 20.1% preterm delivery, 10.5% intrauterine fetal demise and 49.9% live births (Reichman *et al.*, 2009). Thus, pregnant women after ART with this anomaly should be considered high-risk patients.

The unicornuate uterus has no surgical correction (Grimbizis *et al.*, 2001). SET is highly recommended, but there seems to be no indication for cerclage as most of the pregnancy losses occur in the first trimester. Although asymptomatic blind horns can be left untreated, in the case of rudimentary horn with functional endometrium, a prophylactic removal is commonly advised in order to reduce dysmenorrhea, prevent endometriosis and adhesions by retrograde menses, and avoid horn or tubal ectopic gestations (Reichman and Laufer, 2010a; Brucker *et al.*, 2011). However, there is no evidence that this treatment improves reproductive outcomes (Taylor and Gomel, 2008).

## Absence of fusion

There are no specific reports on *didelphys uterus* in ART outcomes. In a meta-analysis, didelphys uterus was not related to decreased conception

rates or increased first- or second-trimester miscarriage, but preterm labor and malpresentation at delivery were increased (Chan et al., 2011b). Similar findings regarding preterm delivery have been described in a retrospective cohort study including 66 956 singleton pregnancies from which 203 (0.3%) presented uterine anomalies (Hua et al., 2011).

Surgical metroplasty should only be considered on a case-by-case basis in women with repeated miscarriages or preterm deliveries (Devi Wold et al., 2006; Reichman and Laufer, 2010a). In the case of obstruction, dyspareunia or infertility due to a co-existing vaginal septum, the septum should be removed (Reichman and Laufer, 2010a).

In women with *bicornuate uterus*, Guirgis and Shrivastav (1990) described the fertility outcome of 14 women with bicornuate uterus who underwent 30 gamete intra-fallopian transfer (GIFT) procedures. Eight women conceived, two of them twice, with five at term and three preterm deliveries. These outcomes were similar to the remaining infertile population treated in their center. However, the incidence of preterm labor appeared to be increased in the affected group.

Spontaneous conception rates do not seem to be decreased, but first and second trimester miscarriage, preterm labor and malpresentation at delivery are increased (Saravelos et al., 2010; Chan et al., 2011b).

The bicornuate uterus rarely requires surgical treatment. In fact, Kirk et al. (1993) showed similar reproductive outcomes in women with bicornuate uterus treated with metroplasty compared with those without surgical intervention.

Cesarean section is often advised in pregnancies obtained after metroplasty (Reichman and Laufer, 2010a) as well as cervical cerclage, although there is no solid evidence to support this assumption (Brucker et al., 2011). SET is highly recommended, and the replacement should be performed in the uterine cavity, which has better ultrasound endometrial appearance and capacity, and easier access for the embryo transfer catheter (Letterie, 2011).

### Abnormal resorption

The septate uterus is the most common anomaly found in infertile women requiring ART. Some studies have shown a significant reduction in IRs and PRs and higher abortion rates in women with septate uterus in comparison to the general infertile population undergoing IVF (Dicker et al., 1996; Lavergne et al., 1996). Incomplete septum also seems to carry a poor prognosis (Ozgur et al., 2007). Tomaževič et al. (2010) performed a retrospective matched-control study in IVF/ICSI patients analyzing 289 embryo transfer before HSC (113 with larger septum and 176 with small partial septum), and 538 embryo transfer following HSC (275 with a large septum and 263 with small partial septum). A control group consisted of 1654 embryo transfers with normal uterus. They found increased MR in non-operated patients (77.1 versus 16.7%, $P < 0.001$), which were reduced to similar values after surgery (29.2 versus 18.4%). Similarly, PRs and live birth rates before HSC were significantly reduced (by 2–3 times and by 9–10 times, respectively) compared with controls, and normalized in operated patients. Results included women with large or small septa, which suggest that shorter septum lengths also carry a poor reproductive prognosis. However, despite these impressive results in favor of surgery before IVF/ICSI, pregnancy and live birth rates remained low (<15–20% and ≤3%, respectively) and MRs were high (77%) in non-operated patients compared with other published data, and therefore these results should be interpreted with caution. Others have not found lower PRs, but have observed increased miscarriage and reduced term delivery rates in women with uncorrected septate and bicornuate uterus undergoing IVF (Marcus et al., 1996; Jayaprakasan et al., 2011).

Hysteroscopic metroplasty may improve pregnancy outcomes due to a reduction of miscarriage, preterm delivery and fetal death, although its benefit in infertile patients is more controversial (Brucker et al., 2011). Thus, pregnancy complications are the main reason for recommending removal of complete or incomplete uterine septum before ART (Brucker et al., 2011; Letterie, 2011; Revel, 2012). ART following HSC of incomplete septae should be performed after 4–6 weeks, which is the time required for wound healing (Brucker et al., 2011). A second look with HSC or at least a three-dimensional (3D) TVS before embryo transfer is advisable to rule out IUAs at the site of dissection (Letterie, 2011). SET is recommended to reduce the risk of preterm delivery.

The *arcuate uterus* is considered a subtle abnormality or a normal variant with minimal or no clinical significance (Olpin and Heilbrun, 2009; Letterie, 2011; Revel, 2012). Its surgical correction is therefore not advised (Reichman and Laufer, 2010a), and treatment is usually expectant (Devi Wold et al., 2006).

Some authors (Tomaževič et al., 2010) have described reduced pregnancy and live birth rates, and high miscarriage and preterm delivery rates, after IVF/ICSI in women with non-operated arcuate uterus. However, they included septa of 1.3–1.5 cm in length, larger than the maximum 1 cm of indentation that is usually accepted as the cut-off value for differentiating between arcuate and septate (subseptate) uterus (Revel, 2012).

Moreover, others (Jayaprakasan et al., 2011) have shown similar MRs in women with arcuate or normal uterus after ART, and have even observed that a small residual septum of <1 cm after HSC does not impair reproductive outcomes in spontaneous conception (Fedele et al., 1996), reinforcing a positive prognosis of the arcuate uterus. Nevertheless, an increased risk of malpresentation at delivery and second-trimester miscarriage has been described (Chan et al., 2011b).

The *T-shaped uterus* is characteristic of women exposed *in utero* to diethylstilbestrol (DES), with the T-shape uterus being the most common anomaly (70%). The T-shape uterus is present in 0.03% of the general/fertile population and in 0.4% of women with recurrent miscarriage, but the prevalence in the infertile population is unknown (Saravelos et al., 2008).

Karande et al. (1990) analyzed 46 infertile women with a history of *in utero* DES exposure who underwent 149 stimulation attempts for IVF. The ongoing PR was significantly lower in this group of patients than in a control group of women with tubal factor infertility. Muasher et al. (1984) analyzed 17 infertile women also exposed *in utero* to DES who underwent 25 stimulated cycles for IVF. PRs of 23.5% per patient and 19% per embryo transfer were obtained, but no control group was compared. In spontaneous conception, a 2-fold increased risk of miscarriage can be expected in the T-shaped uterus (Goldberg and Falcone, 1999). Cervical incompetence and preterm delivery are also frequent.

## Uterine vascularization

Different ultrasonographic parameters have been proposed to evaluate ER, including uterine blood flow measurements using Doppler technology (Raine-Fenning, 2008). Doppler evaluation has been performed on uterine arteries and endometrial/subendometrial vessels. Different

color Doppler signals have been assessed in a number of vessels employing a variety of flow indices in different moments of the ART treatment cycle. These are often correlated with different outcome parameters, and this heterogeneity therefore substantially limits the validity of the conclusions obtained.

*Uterine arteries* have been assessed by Doppler at different time points along the IVF cycle, including prior to or during COH, on the day of hCG administration, oocyte retrieval embryo transfer, or the luteal phase, with conflicting results at all these time points.

For instance, Ozturk *et al.* (2004) showed a very low chance of achieving pregnancy after IVF when the uterine artery pulsatility index (PI) was >3.26 on the day before hCG administration, with a sensitivity of 100% and a specificity of 59%. Cacciatore *et al.* (1996) also showed that with a PI >3.3 and resistance index (RI) >0.95 on the day of embryo transfer, PRs were 10% in comparison to the overall PR of 35%, although this high impedance was only detected in 9% of non-conception cycles.

Hoozemans *et al.* (2008) prospectively assessed uterine artery PI in 102 women in six different stages of the IVF cycle. They found similar values in women with ongoing pregnancy, miscarriage or no pregnancy. The OR for PI was not significant in a multivariate logistic regression analysis, indicating that the amount of decrease of PI did not discriminate between cycles that resulted in pregnancy and cycles that did not, regardless of other variables in the model. Similarly, receiver operating characteristic curves on different cycle days indicated the poor sensitivity and specificity of PI as an implantation marker, with areas under the curve (AUC) between 0.41 and 0.53. Similar conclusions were drawn when frozen-thawed embryo transfer were analyzed (Isaksson *et al.*, 2000).

The wide overlap of values between conception and non-conception cycles (Bloechle *et al.*, 1997) makes the Doppler assessment of the uterine arteries of poor or no clinical value for prospectively discriminating patients who may or may not become pregnant.

*The endometrial and subendometrial* vascularization have been assessed at the same time points of the IVF procedure as uterine arteries, with conflicting data reported. Wang *et al.* (2010) described lower PI, RI and the ratio between peak systolic flow and lowest diastolic flow (S/D) of spiral arteries 8 h before hCG administration in intrauterine pregnancies with live fetus compared with non-pregnant women or those with non-viable pregnancies (biochemical, miscarriage, ectopic or embryonic diapause). They determined the value of color Doppler imaging in predicting IVF-ET outcomes (clinical pregnancy and intrauterine living embryos) and found AUC of endometrial S/D, PI and RI to be 0.694, 0.649 and 0.685, respectively. Considering cut-off values of S/D >3, PI >1.2 and RI >0.7, they described sensitivities, specificities, PPVs and NPVs of 60.5–67.3%, 79.4–88.1%, 45–57.4% and 58.7–79.6%, respectively.

Mercé *et al.* (2008) analyzed 80 patients undergoing IVF and reported a higher Vascularization Index (VI), Flow Index (FI) and Vascularization Flow Index (VFI) in pregnant than in non-pregnant women. They described better AUC for VI (0.724), FI (0.828) and VFI (0.800) in endometrial and subendometrial vessels on the day of hCG administration when no grade 1 or a single grade 1 embryo was transferred. However, poorer AUC (0.342–0.46) was detected for the same Doppler indices when more than one grade 1 embryo was transferred, indicating that the 3D Power Doppler implantation markers were particularly informative of pregnancy when the transferred embryos were of low quality. Similarly, the absence of sub- and intra-endometrial color signal on the day of embryo transfer has been also related to an 8-fold reduction in PRs (Maugey-Laulom *et al.*, 2002).

Ng *et al.* used 3D Power Doppler on the day of oocyte retrieval in women undergoing IVF, in stimulated (Ng *et al.*, 2006a, 2007a) or frozen-thawed embryo transfer cycles (Ng *et al.*, 2006b, 2007a), to predict conception (Ng *et al.*, 2006a, b) or live birth/miscarriage (Ng *et al.*, 2007a). In all these studies, some endometrial or subendometrial Doppler indices were more related to favorable outcomes, but their predictive value was poor. When ROC curve analyses were performed, AUC were around 0.5 for most Doppler indices and <0.65 for the most predictive ones.

In summary, the value of Doppler assessment of uterine blood flow for predicting pregnancy after IVF-ET remains uncertain. Even in studies in which differences have been found between pregnant and non-pregnant women, an overlapping of values has been commonly described (Cacciatore *et al.*, 1996; Bloechle *et al.*, 1997; Puerto *et al.*, 2003). Despite the fact that ultrasonographic parameters for ER seem to be reproducible and comparable in two consecutive IVF cycles (Ng *et al.*, 2007b), Doppler examination is highly dependent on the sonographer's experience and performance. In addition, published studies have included small numbers of subjects, different stimulation protocols, and different study groups and designs, which increases the level of heterogeneity. Doppler uterine assessment is therefore not commonly considered to be clinically helpful or relevant (Bloechle *et al.*, 1997) due to the lack of adequate predictive ability of the IVF outcome (Schild *et al.*, 2001).

Some drugs have been assessed to improve the uterine blood flow in patients with poor vascularization. Sher and Fisch (2000) published a preliminary report of four patients with prior failed ART cycles in whom sildenafil citrate reduced the uterine artery PI after 7 days of treatment, and increased Eth when combined with estradiol valerate. However, Ohl *et al.* (2002) performed an RCT comparing nitroglycerin—an NO donor—as a vasodilating agent with a placebo in 138 IVF patients with a history of implantation failure. Drugs were administered from the day before embryo transfer until either the results of the pregnancy test or menstruation. No differences were found in IR and PR, or in uterine Doppler findings.

Three RCTs have been published evaluating the effects of aspirin. Rubinstein *et al.* (1999) treated 149 women with a daily dose of 100 mg, with an additional 149 controls receiving placebo. Aspirin reduced uterine artery PI, improved ovarian response, and increased IRs and PRs. Lok *et al.* (2004) studied 60 poor responders who received 80 mg/day of aspirin or placebo. No significant differences were found in either intraovarian or uterine artery PI measured at baseline and on the day of hCG administration, nor in ovarian response. Haapsamo *et al.* (2009) included 61 women receiving 100 mg/day of aspirin and another 61 women receiving placebo. Uterine artery PI values measured on the day of embryo transfer were similar in both groups, as were implantation, pregnancy, miscarriage and live birth rates. Mean uterine artery PI values were also similar between women who conceived and those who did not. Arcuate, radial or spiral artery values assessed on the day of embryo transfer did not differ between groups either. However, a non-optimal uterine hemodynamics pattern, defined as bilateral uterine artery PI ≥ 3, was less frequent in the aspirin group. None of the women with this vascular pattern conceived.

Similarly, a previous study (Kuo *et al.*, 1997) examined women with UI or repeated implantation failure (RIF) and an impaired uterine perfusion

(defined as PI ≥ 3) during the menstrual cycle. They found that these women presented an improved blood perfusion on the day of LH peak and in the midluteal phase (peri-implantation period) when they were treated with aspirin (100 mg/day) from Day 3 of the next ovulatory cycle.

Better-designed trials with aspirin or other drugs are needed in IVF to clarify their role in the improvement of uterine blood flow and live birth rates.

## The apparently normal uterus

Most of the pathologies discussed above lack conclusive data regarding their actual role in poor ART outcomes. Moreover, it is not unusual to see uteri that have a non-treatable pathological finding which appear absolutely normal in morphology. In this context, an analysis of ER prior to attempting an embryo transfer appears mandatory.

ER is a transient status of the luminal epithelium that allows blastocyst attachment, the gate-keeper of the implantation process. This is followed by decidualisation, which consists of the differentiation of stromal cells into specialized decidual cells that modulate the invasion of the trophoblast (Cha *et al.*, 2013). Appropriate ER governs embryo adhesion, while decidualisation directs placentation.

The human endometrium is receptive to embryo implantation during a narrow time frame of the menstrual cycle referred to as the WOI. The master regulators for the acquisition of ER are estradiol and progesterone. Progesterone receptors (PR-A and PR-B) and estrogen receptors (ERα and ERβ) are expressed in the human endometrium in the epithelial and stromal compartments. ERα is the primary mediator of estrogen activity in the uterus during implantation (Lubahn *et al.*, 1993). Mice missing both PR-A and PR-B are also infertile and have multiple ovarian and uterine defects. Only PR-B-deficient mice show normal fertility (Lydon *et al.*, 1995; Mulac-Jericevic *et al.*, 2000), indicating that PR-A is the key player. ER and PR signaling during implantation are executed by juxtacrine, paracrine and autocrine factors, which are orchestrated by various growth factors, cytokines, lipid mediators, homeobox transcription factors and morphogens (Wang and Dei, 2006).

Understanding the 'molecular clock' at play during the WOI could help to identify biomarkers of ER that are useful for creating an objective diagnostic test for this still orphan function. In humans, the secretory endometrium has typically been diagnosed by histological characteristics known as the Noyes criteria (Noyes *et al.*, 1975). However, its accuracy, objectivity and relevance for predicting ER have been questioned (Coutifaris *et al.*, 2004; Murray *et al.*, 2004). Also, typical ultrasound features, even with Doppler, are not sufficient for defining ER, as previously discussed.

The search for specific biomarkers that define the WOI has been ongoing for the last two decades. Ultrastructural changes of the endometrial epithelium include phenotype modifications of the plasma membrane (Murphy, 2004) and cytoskeleton (Martín *et al.*, 2000). The presence of pinopodes was proposed as a receptivity marker (Nikas, 1999), but these ectoplasmic epithelial projections are not specific to the receptive state (Quinn and Casper, 2009). Biochemical markers, such as integrins (Lessey *et al.*, 1992), mucin 1 (Meseguer *et al.*, 1998), IL-1 (Simón *et al.*, 1994), calcitonin (Kumar *et al.*, 1998), LIF (Stewart *et al.*, 1992) and HOXA10 (Taylor *et al.*, 1999), initially generated interest, but none of them have proved to be effective for diagnosis in clinical practice.

The transcriptomic signature of ER has been translated to the clinical practice as the endometrial receptivity array (ERA®). ERA is based on the gene expression profile of 238 genes that constitute the ER gene signature derived from an endometrial biopsy (Díaz-Gimeno *et al.*, 2011). It is more accurate than histological dating, and is highly reproducible, even up to 40 months later (Díaz-Gimeno *et al.*, 2013). This test identifies the 'personalized' WOI (pWOI), and has been employed in clinical practice in women with RIF to guide the time frame for personalized embryo transfer (pET) (Ruiz-Alonso *et al.*, 2013). In this study, we found that one in four patients with RIF had a displaced WOI, and their incapacity to implant was attributed to individual variability of the endometrial factor. The 'non-receptive' diagnosis indicates that the endometrium is not ready for blastocyst adhesion, making embryo transfer futile at the moment (Fig. 4). Although it has been assumed that the WOI is constant for all women, this genetic tool demonstrated that it is possible to diagnose the pWOI which can be subsequently used to guide pET. This strategy in patients with RIF of endometrial origin can help to normalize their reproductive outcome (Ruiz-Alonso *et al.*, 2013, 2014). Although initial results are promising, a RCT on the effectiveness of this test is ongoing to properly test its clinical relevance (ClinicalTrials.gov Identifier: NCT01954758).

Uterine fluid collection is less invasive than tissue biopsy. Potential transcriptomic markers of ER have also been investigated in uterine secretions (van der Gaast *et al.*, 2003; Hannan *et al.*, 2010; Cheong *et al.*, 2013; Vilella *et al.*, 2013). Chan *et al.* (2013) were able to classify prereceptive and receptive stages into two distinct clusters, which were potentially capable of predicting implantation. They described 245 genes differentially expressed at day LH+7 and 53 candidate genes for implantation. No follow-up clinical study has been carried out to date.

Proteomics of the uterine fluid is complex since it comprises >90% serum proteins, including albumin, globulins and hemoglobin. These proteins must be removed in order to understand which proteome is relevant to the WOI. Although Hannan *et al.* (2010) studied endometrial aspirates before embryo transfer with a multiplex immunoassay for 17 soluble targets, the predictive value of this method was not sufficiently discriminatory in clinical practice.

Metabolomics, in particular lipidomics, has been investigated in the endometrial fluid. Lipidomics is the large-scale study of lipids and their related networks. Lipids play important roles in diverse biologic functions, from being a primary energy reservoir (triglycerides), to aiding in cell membrane formation (i.e. the phospholipids of lipid bilayers). More specifically, a pilot clinical study investigating relevant predictors of ER found that both PGE2 and PGF2a were significantly increased in uterine fluid during the WOI (Vilella *et al.*, 2013).

In apparently normal uteri with failed implantation, many investigators have proposed endometrial scratching of the endometrium, for example with biopsy or curettage, to improve endometrial receptivity. However, this strategy still lacks convincing clinical data and the biological plausibility for it to be adopted (Simón and Bellver, 2014).

Numerous other investigators have focused their attention on the immunological component of implantation failure when the uterus seems morphologically normal. This is based on the observation that an increase in the number or activity of natural killer (NK) cells can lead to RIF. In this direction, many reports have been published on the use of immunomodulatory therapies to improve ART outcomes, in particular those using intravenous immunoglobulins (IVIg) and prednisolone.

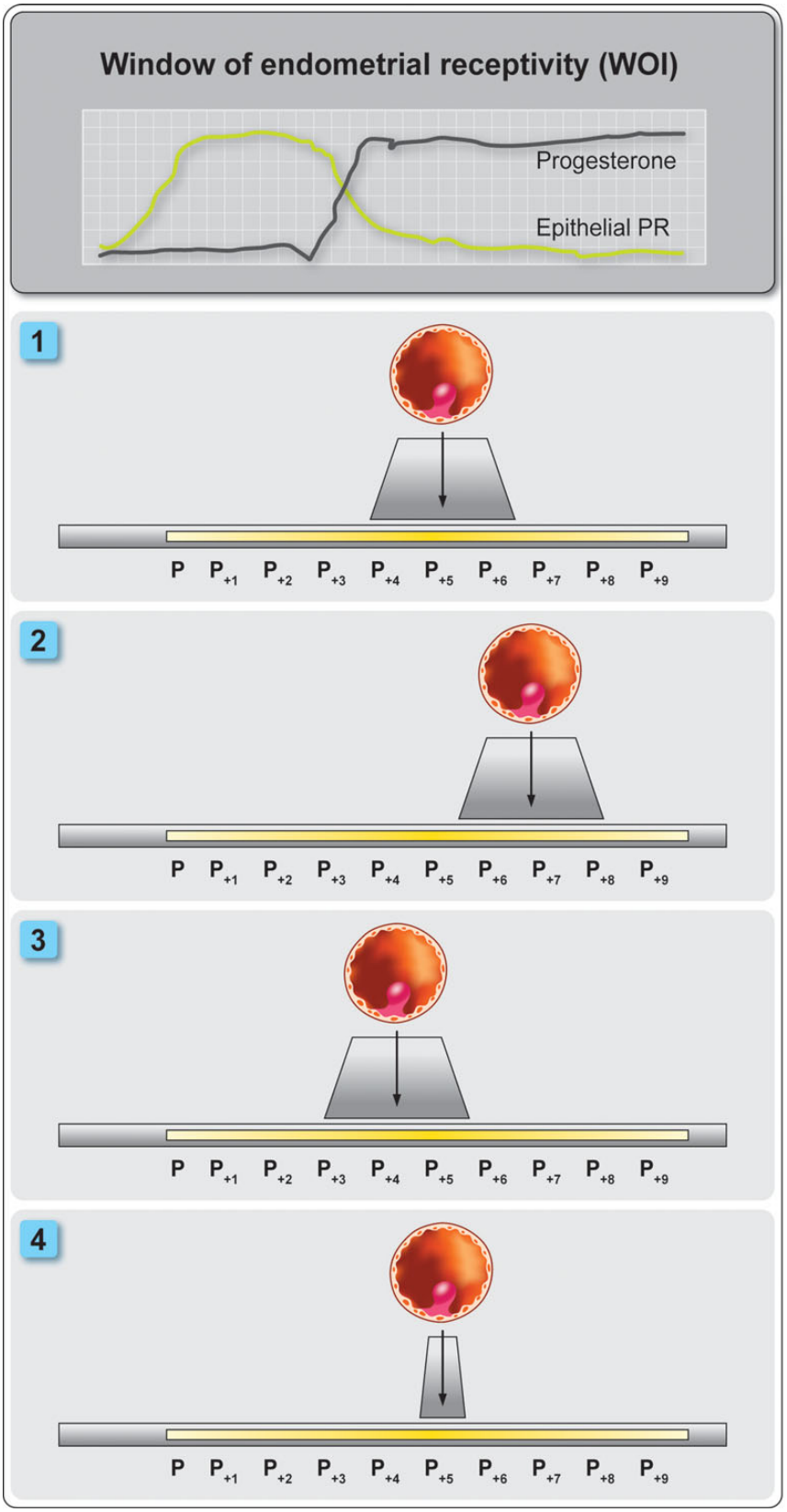


**Figure 4** Displacement of the window of implantation (WOI). It has been assumed that the WOI is constant in time in all women (1). However, the genomic signature of the endometrium demonstrates the existence of a displacement of the WOI in up to 25% of patients that can be delayed (2), advanced (3) or shorter than expected (4). '$P_{+x}$' refers to the days after progesterone administration.

**Table I Grading of Recommendations Assessment, Development and Evaluation (GRADE) scores on evidence available regarding the different causes of uterine infertility and their treatments.**

| Uterine structure | Quality of evidence regarding different uterine pathologies and their impact on live birth rate after ART | | Quality of evidence and grade of recommendation of uterine treatments aimed at improving live birth rates after ART | | Additional recommendation for ART cycle |
|---|---|---|---|---|---|
| **Endometrium** | | | **Evidence** | **Recommendation** | |
| | Endometrial appearance | ⊕ | Sildenafil: ⊕<br>Pentoxyphylline+Vit E: ⊕<br>Estradiol: ⊕<br>G-CSF: ⊕ | ▲?<br>▲?<br>▲?<br>▼▼ | See also 'Vascularization' below |
| | Polyps | ⊕ | Polypectomy: ⊕ | ▲? | |
| | Asherman/atrophy | ⊕ | Adhesiolysis: ⊕<br>Adhesion prevention: Expectant management ⊕<br>Medical curettage: ⊕<br>Adhesion barriers: ⊕⊕⊕/⊕⊕<br>IUD: ⊕<br>Foley: ⊕<br>Amnion: ⊕⊕<br>Estradiol: ⊕<br>Antibiotics: ⊕ | ▲?<br>▲?<br>▲?<br>▲?<br>▲?<br>▲?<br>▲?<br>▲? | |
| | Infections | ⊕ | Antibiotic treatment: ⊕ | ▲? | |
| **Myometrium** | | | **Evidence** | **Recommendation** | |
| | Intramural fibroids | ⊕ | Myomectomy: ⊕<br>Hormonal treatments: ⊕<br>UAE: ⊕<br>MRgFUS: ⊕<br>RF: ⊕ | ▲?<br>▲?<br>▼▼<br>▼▼<br>▼▼ | SET if endometrial cavity affected during myomectomy |
| | Adenomyosis | ⊕ | GnRH analogs: ⊕<br>Surgical management: ⊕ | ▲?<br>▼▼ | |
| | Hyperperistaltism | ⊕ | Cervical closing: ⊕<br>Progesterone: ⊕ | ▲?<br>▲? | |
| **Size and shape** | | | **Evidence** | **Recommendation** | |
| Absence of development | Agenesia | ⊕⊕⊕⊕* | Surrogacy: ⊕⊕⊕⊕*<br>Uterus transplantation: ⊕ | ▲▲<br>▼▼ | Adoption is the non-medical alternative in countries where surrogacy is not legal |
| | Hypoplasia | ⊕ | HRT: ⊕ | ▲? | SET |
| | Unicornuate | ⊕ | Cerclage: ⊕ | ▼▼ | SET |
| Abnormal fusion | Didelphys | ⊕ | Metroplasty: ⊕<br>Cerclage: ⊕ | ▼▼<br>▼▼ | SET |
| | Bicornuate | ⊕ | Metroplasty: ⊕<br>Cerclage: ⊕ | ▲▼<br>▼▼ | SET |
| Absence of resorption | Septate | ⊕ | Septoplasty: ⊕<br>Cerclage: ⊕ | ▲?<br>▼▼ | SET |
| | Arcuate | | Septoplasty: ⊕ | ▼▼ | |
| DES-related abnormality | T-shaped uterus | ⊕ | Cerclage: ⊕ | ▼▼ | SET |
| **Vascular supply** | | | **Evidence** | **Recommendation** | |
| | | ⊕ | Nitroglycerin: ⊕<br>Aspirin: ⊕<br>Sildenafil: ⊕ | ▼▼<br>▲?<br>▼▼ | |

*Continued*

**Table I** *Continued*

| Uterine structure | Quality of evidence regarding different uterine pathologies and their impact on live birth rate after ART | Quality of evidence and grade of recommendation of uterine treatments aimed at improving live birth rates after ART | | Additional recommendation for ART cycle |
|---|---|---|---|---|
| **The 'normal' uterus** | | **Evidence** | **Recommendation** | |
| | | ERA: ⊕⊕ | ▲? | |
| | | Endometrial injury: ⊕⊕ | ▲? | |

ART, assisted reproduction technologies; CHA, cross-linked hyaluronic acid; DES, diethylstilbestrol; ERA, endometrial receptivity assay; G-CSF, granulocyte colony-stimulating factor; MRgFUS, MRI-guided focused ultrasound; HRT, hormonal replacement therapy; IUD, intrauterine device; UAE, uterine artery embolization; RF, radiofrequency; SET, single embryo transfer.
GRADE Score for quality of evidence:
⊕⊕⊕⊕ High quality—Further research is very unlikely to change our confidence in the estimate of effect.
⊕⊕⊕ Moderate quality—Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
⊕⊕ Low quality—Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
⊕ Very low quality or no evidence available—Any estimate of effect is very uncertain.
GRADE Score for strength of recommendations:
▲▲ Strong recommendation for using an intervention.
▲? Weak recommendation for using an intervention.
▼? Weak recommendation against using an intervention.
▼▼ Strong recommendation against using an intervention.

A recent systematic review and meta-analysis did not support the use of adjuvant treatments in women found to have elevated numbers or activity of NK cells undergoing ART, and again highlights the poor quality of the available evidence (Polanski *et al.*, 2014).

## An integrated approach for evaluating the uterus in women undergoing art

An analysis of the different abnormalities found in the uterus shows that their influence on ART is small or very small (Table I). However, it seems likely that this is due to the lack of well-designed studies, as practical experience tells us that many of them must interfere with implantation to a certain extent. When office-based HSC was performed in women undergoing their first ART attempt, the incidence of uterine abnormalities ranged between 11 and 22%, which affected overall outcomes if not corrected (Fatemi *et al.*, 2010; Karayalçin *et al.*, 2012). When the study population consisted of women with RIF, the incidence of uterine defects increased to 26–45% (Kilic *et al.*, 2013). The most reported uterine abnormalities are endometrial polyps, small fibroids, septae and adhesions (Karayalçin *et al.*, 2012; Kilic *et al.*, 2013).

Hysterosalpingography (HSG), two-dimensional TVS, or both, during the infertility work-up should reveal these abnormalities. However, studies have shown that HSG has a sensitivity of 21.6% and false negative rate of 78.4%, with an agreement between HSG and HSC of only 68.9% (Taskin *et al.*, 2011). Similarly, others have shown that HSC had significantly higher sensitivity (97.26 versus 89.04%) and specificity (92 versus 56%) than TVS (Grimbizis *et al.*, 2010). Thus, neither HSG nor 2D TVS are adequate substitutes for HSC. Moreover, in a study including 2500 consecutive HSCs before IVF, 22% were found to have uterine defects that were not detected by HSG or 2D TVS within 1 month of starting the IVF cycle (Karayalçin *et al.*, 2012).

Although modern flexible and thin fibroscopes can make HSC simpler and patient-friendly with success rates >95% (El-Mazny *et al.*, 2011), there is still resistance by many who consider it a surgical endoscopy. Most of the ultrasound machines have incorporated 3D. Negm *et al.* (2012) performed a comparative cross-sectional observational study including 143 RIF patients using 3D TVS plus 3D TVS and Saline Sonohisterosalpingography (SIS) followed by office HSC. They found a substantial degree of concordance between 3D TVS+SIS and HSC ($k = 0.77$; 95% CI 0.6–0.84). Moreover, 3D TVS was a shorter and more patient-friendly procedure than HSC. Thus, 3D TVS should be employed in the diagnosis of uterine malformations (Saravelos *et al.*, 2008; Chan *et al.*, 2011a), and 3D-SIS adds additional accuracy in the diagnosis of EPs (La Torre *et al.*, 1999; Makris *et al.*, 2007) and IUAs (Sylvestre *et al.*, 2003).

Despite the low degree of evidence demonstrating that uterine abnormalities may impair success, we recommend a careful study of the uterus prior to commencing an ART cycle. This integrated approach makes a distinction between couples undergoing ART for the first time, and couples suspected to have RIF, even in the presence of a morphologically normal uterus (Figs 5 and 6).

There is no standard definition of implantation failure. Our own database analyzing >21 000 IVF cycles showed that the replacement of up to five embryos was associated with a continuous increase in live birth rates (Garrido *et al.*, 2011). Increasing the number of embryos replaced also improved outcomes, although the slope of the curve showed a clear difficulty in achieving pregnancies to term.

Patients should undergo a 3D TVS plus SIS to carefully explore the uterine cavity (Fig. 5). If the cavity looks normal, the ART cycle should proceed. If a morphologic abnormality is observed, medical or surgical treatment is advised as appropriate, although the evidence is weak for the majority of the alternatives addressed herein.

In cases where the uterine appearance is normal or there is no convincing evidence of a positive response to treatment, a thorough evaluation

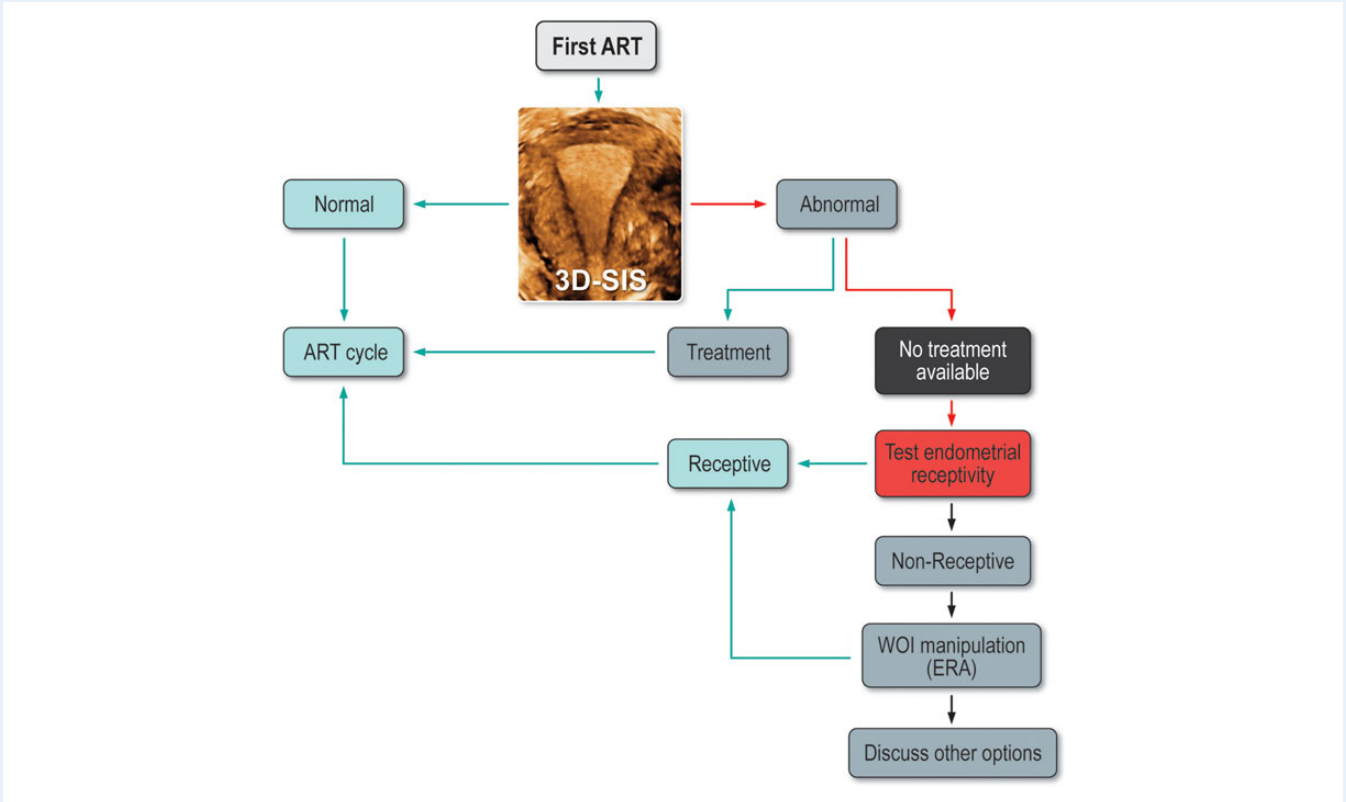


**Figure 5** Flow-chart diagram for the study of the uterine factor in women undergoing their first ART cycle. 3D-SIS, 3D-saline sonohysterosalpingography; ERA, endometrial receptivity array.

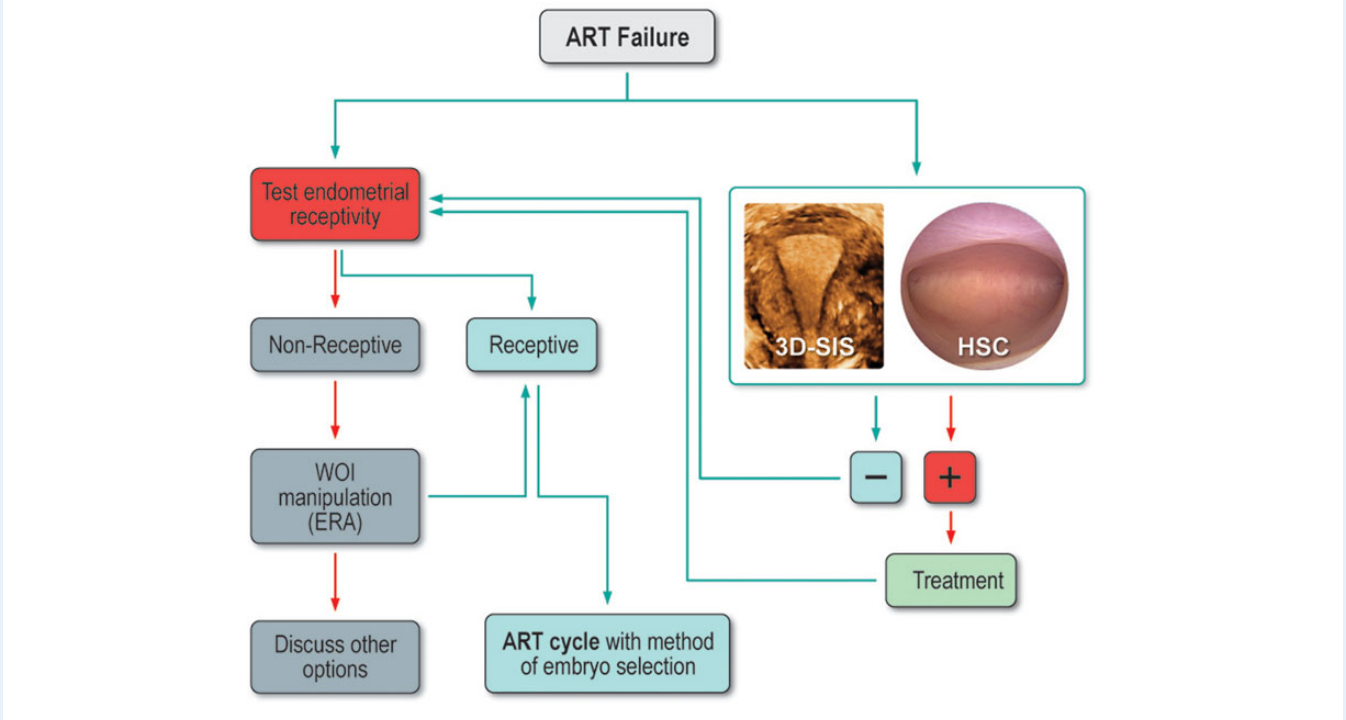


**Figure 6** Flow-chart diagram for the study of the uterine factor in women undergoing ART after several failed attempts. HSC, hysteroscopy.

of ER seems advisable before attempting ART. The perfect test for ER awaits further research but, whatever the method employed, the crucial step is to test the ability of the endometrium to sustain a pregnancy, even in situations where the morphological signs are unfavorable. If the endometrial functional test turns out to be normal, we would advise the couple to proceed with the ART cycle. In case of abnormality, then a thorough discussion with the couple is needed before attempting ART, but there is currently no reason to cancel an ART treatment.

Couples with RIF represent a different population. As Fig. 6 shows, we always advise a thorough morphological (3D TVS+SIS) and functional (analysis of ER) study of the uterus before attempting a new ART cycle. Given the high incidence of embryo abnormalities in these couples (Rubio *et al.*, 2013), however, a method of embryo selection, which looks for the replacement of viable embryos, is highly recommended. New methods of embryo selection through comprehensive chromosome screening have recently been introduced, but have only been tested in good prognosis patients (Yang *et al.*, 2012; Scott *et al.*, 2013). In this field, well-conducted RCTs are also necessary, but the final message is to pay attention not only to the embryo, but also to the uterus.

## Supplementary data

Supplementary data are available at http://humupd.oxfordjournals.org/.

## Authors' roles

Conception and organization of manuscript: D.G. and A.P.; literature search and analysis of evidence: D.G., C.D.-G. and A.P.; writing and editing: D.G., J.B., C.S. and A.P.

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C.S. and A.P. are IVIOMICS shareholders. D.G., J.B. and C.D.-G. have nothing to disclose.

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