

# Implantation failure: molecular mechanisms and clinical treatment

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Submitted on February 21, 2010; resubmitted on July 19, 2010; accepted on July 26, 2010

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**BACKGROUND:** Implantation is a complex initial step in the establishment of a successful pregnancy. Although embryo quality is an important determinant of implantation, temporally coordinated differentiation of endometrial cells to attain uterine receptivity and a synchronized dialog between maternal and embryonic tissues are crucial. The exact mechanism of implantation failure is still poorly understood.

**METHODS:** This review summarizes the current knowledge about the proposed mechanisms of implantation failure in gynecological diseases, the evaluation of endometrial receptivity and the treatment methods to improve implantation.

**RESULTS:** The absence or suppression of molecules essential for endometrial receptivity results in decreased implantation rates in animal models and gynecological diseases, including endometriosis, hydrosalpinx, leiomyoma and polycystic ovarian syndrome. The mechanisms are diverse and include abnormal cytokine and hormonal signaling as well as epigenetic alterations.

**CONCLUSIONS:** Optimizing endometrial receptivity in fertility treatment will improve success rates. Evaluation of implantation markers may help to predict pregnancy outcome and detect occult implantation deficiency. Treating the underlying gynecological disease with medical or surgical interventions is the optimal current therapy. Manipulating the expression of key endometrial genes with gene or stem cell-based therapies may some day be used to further improve implantation rates.

**Key words:** implantation / *HOX* genes / endometriosis / hydrosalpinx / leiomyoma

## Introduction

Embryo implantation represents a critical step of the reproductive process and consists of a unique biological phenomenon. The blastocyst comes into intimate contact with the endometrium and forms the placenta that will provide an interface between the growing fetus and the maternal circulation (Guzeloglu-Kayisli *et al.*, 2009). Successful implantation requires a receptive endometrium, a functional embryo at the blastocyst developmental stage and a synchronized dialog between maternal and embryonic tissues (Simon *et al.*, 2000). The human endometrium undergoes a complex series of organized proliferative and secretory changes in each menstrual cycle, and exhibits only a short period of receptivity, known as the 'window of implantation' (Strowitzki *et al.*, 2006). The endometrium becomes receptive to blastocyst implantation ~6 days after ovulation and remains receptive for 4 days (cycle days 20–24; Bergh and Navot, 1992). When implantation does not occur, a timely destruction of the fully developed endometrium leads to menstruation. However, if implantation occurs, the endometrium continues to grow and undergoes further morphological and molecular changes to provide sufficient support for the growing embryo (Strowitzki *et al.*, 2006).

Implantation has three stages: apposition, adhesion and penetration. Apposition is an unstable adhesion of the blastocyst to the endometrial surface. During this stage, the trophoblast becomes closely apposed to the luminal epithelium (Tabibzadeh and Babaknia, 1995). This is followed by the adhesion stage in which the association of the trophoblast and the luminal epithelium is sufficiently intimate as to resist dislocation of the blastocyst by flushing the uterine lumen. The first sign of the attachment reaction occurs on Day 20–21 in humans, and it coincides with a localized increase in the stromal vascular permeability at the site of blastocyst attachment (Sharkey and Smith, 2003). Following adhesion, the embryo invades through the luminal epithelium into the stroma to establish a relationship with the maternal vasculature; although this activity is mainly controlled by trophoblasts, the decidua also limits the extent of invasion (Sharkey and Smith, 2003). In response to this invasion and the presence of progesterone stimulation, the endometrial stromal cells and endometrial extracellular matrix undergo decidualization that is essential for the viability of the pregnancy.

Several benign gynecological disorders including endometriosis, hydrosalpinx, leiomyoma and polycystic ovarian syndrome (PCOS) are associated with decreased cycle fecundity and impaired uterine receptivity (Table 1) (Donaghy and Lessey, 2007). This is perhaps best illustrated in the setting of *in vitro* fertilization (IVF). Assisted reproductive technology (ART) tools are now available that enable the selection of high-quality embryos, and ART protocols continue to evolve with the aim of achieving higher pregnancy rates, fewer multiple births as well as healthy babies from genetically affected progenitors. However, despite these advances, implantation rates are still relatively low and have not increased sufficiently in the last decade to allow widespread adoption of single-embryo transfer (Andersen *et al.*, 2005). Uterine receptivity plays a key role in the establishment of successful pregnancies, and its impairment may limit ART success and contribute to the subfertility in previously mentioned gynecological diseases (Donaghy and Lessey, 2007).

This review aims to summarize the current knowledge of the mechanism of implantation, molecular and morphological markers of

endometrial receptivity (see online Supplementary data, Appendix) and proposed mechanisms of implantation failure in gynecological diseases, including endometriosis, hydrosalpinx, leiomyoma, endometrial polyp, adenomyosis, endometritis and PCOS.

## Methods

For this review, we included data and relevant information obtained through a PubMed database search for all articles published in English from 1952 through 2010, which included the terms 'implantation', 'implantation markers', 'endometriosis', 'hydrosalpinx', 'leiomyoma', 'endometrial polyp', 'adenomyosis', 'endometritis' and 'polycystic ovarian syndrome'.

## Roles of homeobox genes in implantation

*HOX* genes are essential for endometrial growth, differentiation and receptivity by mediating some functions of the sex steroids (see online Supplementary data, Appendix) during each reproductive cycle. Both *HOXA10* and *HOXA11* mRNA are expressed in human endometrial epithelial and stromal cells, and their expression is significantly higher in the mid- and late-secretory phases, coinciding with time of embryo implantation and high levels of estrogen and progesterone (Gendron *et al.*, 1997; Taylor *et al.*, 1998, 1999b; Samo *et al.*, 2005). Moreover, in the case of successful implantation, the decidua of the early pregnancy continues to express high levels of *HOXA10* and *HOXA11* mRNA (Taylor *et al.*, 1998, 1999b).

Both estrogen and progesterone act independently and in concert to upregulate *HOXA10* and *HOXA11* expression in endometrium. In endometrial cells, 17 $\beta$ -estradiol and medroxyprogesterone acetate (MPA) significantly increased the *HOXA10* mRNA expression (Taylor *et al.*, 1998). The response to MPA was greater than to 17 $\beta$ -estradiol, and combination treatment of 17 $\beta$ -estradiol and MPA induced higher levels of *HOXA10* mRNA expression compared with treatment with either hormone alone (Taylor *et al.*, 1998). A similar expression pattern of *HOXA11* was also demonstrated in response to estrogen and progesterone in endometrial cells (Taylor *et al.*, 1999b). Furthermore, these effects of estrogen and progesterone are mediated through their cognate receptors binding to the regulatory regions of the *Hoxa10* or *Hoxa11* genes (Couse *et al.*, 2001; Akbas *et al.*, 2004; Martin *et al.*, 2007).

As transcription factors, *HOX* genes regulate other downstream target genes leading to the proper development of the endometrium and receptivity to implantation. Both *Hoxa10* and *Hoxa11* are necessary for fertility in mice. Although *Hoxa10* or *Hoxa11* knockout mice produce a normal number of embryos and these embryos survive in a wild-type surrogate, wild-type embryos from the surrogate mice cannot implant in the *Hoxa10*- and *Hoxa11*-deficient mice, suggesting uterine factor infertility due to an implantation defect (Hsieh-Li *et al.*, 1995; Satokata *et al.*, 1995; Benson *et al.*, 1996). The importance of maternal *Hoxa10* in implantation is further supported by experiments using antisense oligonucleotides to *Hoxa10* that were injected into the mouse uterus and, as a result, implantation rates decreased (Bagot *et al.*, 2000).

A number of molecular and morphological markers (see online Supplementary data, Appendix) specific to the implantation window are regulated by *Hox* genes, including pinopodes,  $\beta$ 3 integrin and

insulin-like growth factor-binding protein-1 (IGFBP-1). Pinopodes are apical cellular protrusions that become visible between Days 20 and 21 of the natural menstrual cycle (Nikas and Aghajanova, 2002). *HOXA10* antisense treatment diminishes pinopod number, whereas an increase is observed when uterine *HOXA10* expression is upregulated (Bagot et al., 2001). Moreover, *HOXA10* has been shown to directly regulate the expression of  $\beta_3$  integrin through a consensus Abd-B type *HOX*-binding site located 5' of the  $\beta_3$ -integrin gene within its regulatory region (Daftary et al., 2002). In baboon and human endometrial stromal cells, *HOXA10* interacts with the FOXO transcription factor FKHR, and together this heterodimer upregulates IGFBP-1 expression (Foucher et al., 2002; Kim et al., 1999, 2007). There are no documented human mutations in *HOXA10* or *HOXA11* likely due to the widespread function of these genes in development and their necessity for reproduction. However, women with decreased expression of either of these two genes during the secretory phase have lower implantation rates as seen in endometriosis, PCOS, hydrosalpinx and fibroids (Taylor et al., 1999a; Cermik et al., 2003; Daftary et al., 2007; Rackow and Taylor, 2010).

## Mechanisms of implantation failure in gynecological diseases

### Endometriosis

Endometriosis is defined by the presence of viable endometrial tissue outside the uterine cavity. The prevalence of endometriosis approaches to 6–10% in the general reproductive age female population and to 25–50% in women with infertility (Houston, 1984). There are multiple proposed mechanisms of subfertility in endometriosis, including altered folliculogenesis, impaired fertilization, defective implantation and poor

oocyte quality, with decreased ability to implant (Tummon et al., 1988; Simon et al., 1994; Ulukus, et al., 2006).

Some studies fail to show any difference between implantation rates in women with and without endometriosis following IVF (Inoue et al., 1992; Dmowski et al., 1995; Olivennes et al., 1995; Pal et al., 1998; Bukulmez et al., 2001). However, others demonstrate statistically significant lower implantation and pregnancy rates in women undergoing IVF with early as well as late stages of the disease (Matson and Yovich, 1986; Barnhart et al., 2002; Kuivasaari et al., 2005). Results from oocyte donation programs have been used in an attempt to understand whether the endometrium or the oocyte or both are affected in endometriosis. In women with endometriosis, donor oocytes obtained from women without the disease implant as efficiently as in other recipients (Simon et al., 1994). Furthermore, reduced pregnancy and implantation rates are observed when oocytes come from donors with endometriosis (Simon et al., 1994; Remohi et al., 1997; Diaz et al., 2000). However, the cases used in these studies do not reflect the general population of endometriosis patients. Firstly, the indication for IVF in these studies is decreased ovarian reserve instead of endometriosis-related infertility. Secondly, the recipients in oocyte donation programs are relatively older compared with women with endometriosis, and endometriosis regresses when women approach to menopause. Therefore, use of results from oocyte donation does not provide a valid model to evaluate implantation and pregnancy rates in young women with infertility related to endometriosis.

A number of implantation markers are aberrantly expressed in patients with endometriosis and may contribute to infertility in some women with endometriosis. In a prospective and double-blind study, 89 endometrial biopsies were taken before a diagnostic laparoscopy; the majority of women with reduced  $\alpha_v\beta_3$  integrin expression during the time of implantation were shown to have stage I or II endometriosis (Lessey et al., 1994). Interestingly, improvement of fertility

**Table I** Proposed mechanisms of implantation failure in gynecological diseases.

Gynecological disease	Proposed mechanism of implantation failure
Endometriosis	Reduced $\alpha_v\beta_3$ integrin and LIF expressions in the window of implantation Lack of IL-11 and IL-11R $\alpha$ expressions in secretory phase Absence of <i>HOXA10</i> and <i>HOXA11</i> peak in secretory phase Elevated <i>EMX2</i> expression Progesterone resistance Alteration in PR-A to PR-B ratio Decreased <i>HOXA10</i> expression due to hypermethylation of its promoter region
Hydrosalpinx	Mechanical interference to apposition by bathing of endometrial lining with hydrosalpinx fluid intermittently Reduced $\alpha_v\beta_3$ integrin and LIF expressions Decreased <i>HOXA10</i> expression
Leiomyoma	Distorting endometrial lining Obstructing the tubal ostia or cervical canal Decreased <i>HOXA10</i> and <i>BTEBI</i> expressions
Endometrial polyp	Mechanical interference with sperm transport and embryo implantation Low IGFBP-1 and osteopontin levels in secretory phase Low progesterone receptor levels in secretory phase
PCOS	Decreased $\alpha_v\beta_3$ integrin, <i>HOXA-10</i> and IGFBP-1 during secretory phase Overexpression of androgen receptors Failure to downregulate estrogen receptor- $\alpha$ in the window of implantation Overexpression of the steroid receptor coactivators AIB1 and TIF2

and return of normal  $\alpha_v\beta_3$  levels are observed after treating women with endometriosis with gonadotrophin-releasing hormone (GnRH) analogs and laser ablation of implants (Lessey and Young, 1997). Additionally, interleukin (IL)-11 and IL-11 receptor- $\alpha$  are not expressed in the endometrium of infertile women with endometriosis (Dimitriadis et al., 2006). Moreover, leukemia inhibitory factor (LIF) expression in eutopic glandular epithelium is significantly lower in infertile women with endometriosis compared with fertile controls (Dimitriadis et al., 2006).

Several studies have demonstrated an attenuated or dysregulated progesterone response at a molecular level in endometrium from women with endometriosis (Metzger et al., 1988; Burney et al., 2007). Alteration in the ratio of progesterone receptor (PR)-A to PR-B was suggested as one of the possible mechanisms of progesterone resistance in endometriosis (Lee et al., 2009). In murine endometriosis model, decreased PR-A mRNA and increased ratio of PR-B to PR-A mRNA and total PR protein expressions were detected in the eutopic endometrium compared with controls (Lee et al., 2009). PR expression was also found to be similarly altered in the eutopic endometrium of baboons with induced endometriosis (Fazleabas et al., 2003). Consistent with these animal models of endometriosis, increased expression of total PR was observed in women with moderate to severe endometriosis (Burney et al., 2007).

Multiple gene expression profiles using microarray analysis in endometrium from women with or without endometriosis showed that a number of progesterone target genes were dysregulated during the window of implantation leading to an inhospitable environment for implanting blastocysts (Kao et al., 2003; Kamat et al., 2004; Burney et al., 2007). Two of the progesterone target genes dysregulated in endometriosis are Hox genes. As discussed earlier, the expression of both *HOXA10* and *HOXA11* rises dramatically during implantation window and remains elevated throughout the rest of the luteal phase (Taylor et al., 1998). However, the increased *HOXA10* and *HOXA11* expression fails to occur in women with endometriosis, and in mice and baboons with induced endometriosis (Taylor et al., 1999a; Kim et al., 2007; Lee et al., 2009). Furthermore, the expression of various other mediators of endometrial receptivity that are also mediated by HOX genes, such as pinopodes,  $\alpha_v\beta_3$  integrin and IGFBP-1, are found to be decreased in endometriosis (Lessey et al., 1994; Klemmt et al., 2006; Vitiello et al., 2007). The expression of the Empty Spiracles homolog 2 (*Emx2/EMX2*) gene that is associated with defective implantation is repressed by elevated levels of *HOXA10* in normal endometrium during the window of implantation (Troy et al., 2003). However, diminished *HOXA10* expression in endometriosis derepresses *EMX2* repression, which manifests as simultaneously elevated levels of endometrial *EMX2* mRNA (Daftary and Taylor, 2004). Consistent with the fact that high peri-implantation endometrial *EMX2* levels are associated with a defective implantation phenotype in patients with endometriosis, there is a significant 40% decrease in the litter size of mice transfected with *EMX2* cDNA in the peri-implantation period (Taylor and Fei, 2005).

Epigenetics refers to any changes in DNA that alter gene expression without altering the DNA sequence. The hallmarks of epigenetic gene regulation are DNA methylation and histone modifications. Both animal and human studies demonstrated *HOXA10* hypermethylation as one of the possible mechanisms by which *HOXA10* levels are decreased in endometriosis (Wu et al., 2005; Kim et al., 2007;

Lee et al., 2009). In both mouse and baboon endometriosis models, hypermethylation of the 5' promoter region of *Hoxa10/HOXA10* and decreased expression of *Hoxa10/HOXA10* genes were demonstrated in eutopic endometrium (Kim et al., 2007; Lee et al., 2009). In humans, three CpG-rich fragments in the *HOXA10* gene were identified (one in the region 50 bp upstream of exon 1 and two in the intronic region). *HOXA10* was hypermethylated in all fragments in the endometrium of women with endometriosis compared with controls (Wu et al., 2005). Moreover, the gene coding for the enzyme that catalyze DNA methylation (i.e. DNA methyltransferase 3A) was upregulated in eutopic endometrium of women with endometriosis (Wu et al., 2007). *HOXA10* hypermethylation permanently silences *HOXA10* gene expression in endometriosis. Given that HOX genes modulate some of the functions of progesterone, decreased *HOXA10* expression due to hypermethylation may result in resistance to progesterone action in endometriotic tissues and impaired implantation. Unfortunately, methylation is relatively irreversible, and the uterine defect may still persist after medical or surgical treatment of endometriosis. This fact likely explains why only modest success in improving infertility is achieved after surgical resection of endometriosis.

In summary, infertility in endometriosis is not exclusively due to poor oocyte quality or embryo development but also the result of defective implantation. Decreased expression of implantation markers during the window of implantation, silencing of the *HOXA10* gene, due to hypermethylation and progesterone resistance may lead to impaired implantation in endometriosis.

## Hydrosalpinx

Hydrosalpinx is described as a distally blocked, dilated, fluid-filled fallopian tube with a heterogeneous spectrum of pathology. The prevalence of hydrosalpinges in patients suffering from tubal disease is relatively common and ranges from 10 to 13% when diagnosed by ultrasound, and up to 30% when diagnosed by hysterosalpingography, laparoscopy or laparotomy (Andersen et al., 1994; Katz et al., 1996; Blazar et al., 1997; Murray et al., 1997). Two meta-analyses have shown that women with hydrosalpinx have lower implantation, pregnancy and delivery rates and a higher incidence of spontaneous miscarriage after IVF-embryo transfer compared with women with tubal infertility of other causes (Zeyneloglu et al., 1998; Camus et al., 1999). Furthermore, a prospective, randomized clinical trial and a Cochrane review have demonstrated improved pregnancy and delivery rates with laparoscopic salpingectomy for hydrosalpinges prior to IVF (Strandell et al., 2001; Johnson et al., 2002). These findings suggest that, besides occluding the fallopian tubes, hydrosalpinx may also affect infertility through other mechanisms. One theory to explain the deleterious effect of a hydrosalpinx on the outcome of IVF is the intermittent bathing of the intrauterine environment with inflammatory fluid within the hydrosalpinx (Kodaman et al., 2004). The hydrosalpinx fluid may also mechanically interfere with the apposition of the implanting embryo (Mansour et al., 1991).

The presence of hydrosalpinx may also reduce the receptivity of the endometrium by decreasing the expression of specific factors. In the presence of hydrosalpinges, the expression of  $\alpha_v\beta_3$  integrin is significantly reduced in the window of implantation when compared with fertile controls, and 70% of the patients with hydrosalpinx who underwent salpingectomy demonstrated return of this marker back to normal levels (Meyer et al., 1997; Bildirici et al., 2001; Savaris et al.,

2006). Similarly, the expression of LIF is lower in the endometrium during the window of implantation in infertile patients with hydrosalpinx, compared with normal fertile patients without hydrosalpinx (Seli *et al.*, 2005). Furthermore, if the hydrosalpinges are removed, the LIF expression returns to normal expression in these patients (Seli *et al.*, 2005). An *in vitro* study, using hydrosalpinx fluid, demonstrated a dose-dependent decrease of HOXA10 mRNA expression in Ishikawa cells, a well-differentiated endometrial adenocarcinoma cell line (Daftary and Taylor, 2002). Likewise, the expression of HOXA10 mRNA was significantly lower in infertile women with hydrosalpinges, compared with fertile controls (Daftary *et al.*, 2007). After salpingectomy, HOXA10 mRNA levels were similar to those of age-matched fertile controls, indicating that salpingectomy restores HOXA10 expression to physiological levels (Daftary *et al.*, 2007).

## Leiomyoma

Uterine leiomyomas are the most common benign tumor in women of reproductive age, and their prevalence approaches to 70% in white women and more than 80% in black women by age 50 years (Day Baird *et al.*, 2003). Leiomyomas are present in ~5–10% of women with infertility and are the sole factor identified in 1–2.4% (Donnez and Jadoul, 2002). Intramural and submucosal leiomyomas can distort the uterine cavity or obstruct the tubal ostia or cervical canal and, thus, may affect fertility (Pritts, 2001). Moreover, in the setting of a distorted uterine cavity caused by leiomyomas, significantly lower IVF pregnancy rates were identified (Pritts, 2001; Surrey *et al.*, 2001). When myomectomies have been performed on women with otherwise unexplained infertility, the subsequent pregnancy rates have been reported to be 40–60% after 1–2 years (Sudik *et al.*, 1996; Campo *et al.*, 2003). There is limited molecular data to explain the mechanism behind these clinical observations. Recent studies demonstrated that leiomyomas may adversely affect the overlying endometrium and impair endometrial receptivity (Matsuzaki *et al.*, 2009; Rackow and Taylor, 2010). Endometrial HOXA10, HOXA11 and BTEB1 (Basic transcription element binding proteins 1, a PR coactivator and a downstream target transcription factor of HOXA10 and HOXA11) expression were found to be significantly decreased in uteri with submucosal myomas compared with controls during the window of implantation (Matsuzaki *et al.*, 2009; Rackow and Taylor, 2010). Moreover, HOXA10 expression was globally affected in the presence of a submucosal myoma rather than focally changed in the endometrium over the myoma (Rackow and Taylor, 2010). Therefore, besides distorting the uterine cavity, submucosal myoma may result in global changes in endometrial receptivity. Further studies are required to further delineate the molecular mechanisms of implantation failure in women with leiomyomas distorting the uterine cavity.

## Endometrial polyp

Endometrial polyps are benign, localized overgrowths of endometrium. The mechanism by which polyps may adversely affect fertility is poorly understood, but may be related to mechanical interference with sperm transport, embryo implantation or aberrant expression of implantation markers. Low IGFBP-1 and osteopontin levels were detected in uterine flushings in mid-luteal phase in patients with endometrial polyps (Ben-Nagi *et al.*, 2009). Moreover, significant increase in their concentrations in uterine flushings was observed following

polypectomy (Ben-Nagi *et al.*, 2009). Endometrial polyps have decreased expression of PRs that may result in progesterone resistance. This may cause abnormalities in the secretion of progesterone-regulated implantation markers (Peng *et al.*, 2009).

Endometrial polyps are identified by hysteroscopy in 16–26% of women with otherwise unexplained infertility and the rate is much higher (46%) in infertile women with endometriosis (Kim *et al.*, 2003; de Sa Rosa e de Silva *et al.*, 2005). The only randomized trial examining the effect of polypectomy on pregnancy rate after intrauterine insemination demonstrated a statistically significant improvement in pregnancy rate in women who underwent hysteroscopic polypectomy compared with those who did not undergo polypectomy (63 versus 28%; Perez-Medina *et al.*, 2005). Three nonrandomized studies also found an association between polypectomy and improved spontaneous pregnancy rates (Varasteh *et al.*, 1999; Spiewankiewicz *et al.*, 2003; Shokeir *et al.*, 2004). The effect of endometrial polyps on IVF remains unclear. Studies suggest that endometrial polyps <2 cm in size appear to have limited impact on IVF outcome. However, further studies are required to examine the effect of larger polyps, polyp location and number of polyps on IVF outcome.

## Adenomyosis

Adenomyosis is a common gynecological disorder with unclear etiology that is characterized by the presence of heterotopic endometrial glands and stroma in the myometrium with adjacent smooth muscle hyperplasia. An association between adenomyosis and subfertility has not been fully established. The presenting symptoms include a soft and diffusely enlarged uterus with menorrhagia, dysmenorrhea and metrorrhagia. Infertility is a less frequent complaint, since uterine adenomyosis is usually diagnosed in the fourth and fifth decade of life. However, since more women delay their first pregnancy until later in their 30 or 40, adenomyosis is encountered more frequently. When adenomyosis is encountered in younger reproductive age women, it is likely to reduce endometrial receptivity in a manner similar to endometriosis. Further studies are required to delineate the molecular mechanisms of implantation failure in women with adenomyosis.

## Polycystic ovarian syndrome

Polycystic ovarian syndrome is a common endocrinological disorder, affecting ~5–7% of women of reproductive age, and characterized by oligo-/amenorrhea due to oligo-/anovulation, polycystic ovaries and elevated circulating concentrations of androgens and/or signs of hyperandrogenism (Azziz *et al.*, 2004). In addition, ~75% of women with PCOS have insulin resistance and hyperinsulinemia (Dunaif, 1997). Infertility associated with PCOS derives from chronic anovulation, and there are increasing data suggesting that implantation failure can further complicate achieving pregnancy in women with this disorder (Giudice, 2006). Although ovulation is readily obtained with medical induction, implantation rates remain lower than fertile controls and early pregnancy loss rates are increased.

In women with PCOS, who are anovulatory or oligo-ovulatory, the regulatory roles of progesterone are suboptimal or absent, and this results in relatively constant unopposed action of estrogen in the endometrium (Giudice, 2006). There is increasing evidence of dysregulated expression of markers of uterine receptivity in endometrium of women with PCOS. In ovulatory PCOS patients,  $\alpha_v\beta_3$  integrin, HOXA-10 and

IGFBP-1 expression is decreased during the secretory phase (Suikkari *et al.*, 1989; Apparao *et al.*, 2002; Cermik *et al.*, 2003). *In vitro* HOXA10 expression was directly decreased by testosterone, suggesting a role for androgen reduction in improving endometrial receptivity.

Women with PCOS also exhibit significant differences in their complement of steroid receptors and coactivators when compared with fertile controls. PCOS endometrium overexpresses androgen receptors and fails to downregulate estrogen receptor- $\alpha$  in the window of implantation (Apparao *et al.*, 2002; Gregory *et al.*, 2002). Moreover, overexpression of the steroid receptor coactivators AIB1 (nuclear receptor coactivator 3) and TIF2 (transcriptional intermediary factor 2) may accentuate the activity of estrogen in endometrial cells from women with PCOS (Gregory *et al.*, 2002). Overall, decreased expression of uterine receptivity markers and dysregulation of steroid receptor expression and activity may contribute to the lower pregnancy rates observed in women with PCOS. However, whether this dysregulation is due to an inadequate progesterone action or excessive androgen/insulin action is not clear at this time.

## Endometritis

Endometritis has been associated with infertility and implantation failure because of the possible action of microbial products on the endometrial receptivity (Devi Wold *et al.*, 2006). Women with chronic endometritis have significantly lower clinical pregnancy and implantation rates (11 and 8%) compared with those with negative biopsies (58 and 31%; Romero *et al.*, 2004). Acute endometritis has been described in ~15% of patients undergoing a hysteroscopic workup before IVF and intracytoplasmic sperm injection and in up to 42% of patients with repeated IVF failure (Feghali *et al.*, 2003). Moreover, a significant increase in pregnancy rates in subsequent IVF cycle was reported on completion of antibiotic treatment (Feghali *et al.*, 2003; Romero *et al.*, 2004).

Acute endometritis is most commonly caused by bacteria. It usually responds well to treatment and is only rarely associated with long-standing infertility. In contrast, chronic endometritis can be caused by a variety of agents such as bacteria, viruses and parasites. There is a strong relationship between genital tuberculosis and infertility. Genital tuberculosis is a rare disease in developed countries, but it represents a frequent cause of chronic pelvic inflammatory disease and infertility in developing countries. It is almost always secondary to a tubercular lesion elsewhere in the body and usually affects women between the ages of 20 and 40 years (Varma, 1991). In most cases of chronic endometritis, no causal pathogen can be isolated, and the inflammation is considered nonspecific. The antibiotic regimen prescribed is, therefore, empirical. No data exist on pregnancy rates after histologically confirmed and subsequently treated nonspecific chronic endometrial inflammation.

## Clinical assessment of endometrium

### Morphological analysis of the endometrium

Ideally, a technique to assess endometrium and thereby predict endometrial receptivity must be easily performable within the daily clinical routine and would preferably be noninvasive. These requirements are

met by ultrasonographic evaluation of endometrial thickness and its echogenic pattern.

Endometrial thickness is defined as the minimal distance between the echogenic interfaces of myometrium and endometrium, measured in the plane through the central longitudinal axis of the uterine body. Increased endometrial thickness is associated with improved pregnancy rates in IVF–embryo transfer cycles (Zhang *et al.*, 2005). The data extracted from the donor oocyte programs suggest that a pregnancy cannot be achieved if the endometrium thickness is below a certain critical cutoff limit. Although there are studies revealing that the thickness of endometrium for a successful implantation can be as thin as 4 mm (Noyes *et al.*, 1995; Sundstrom, 1998; Check *et al.*, 2003a, b); for the majority of the cases, at least 6 mm of endometrial thickness is prerequisite for a successful implantation (Alam *et al.*, 1993; Coulam *et al.*, 1994). However, no correlation was demonstrated between endometrial histology and endometrial thickness either in spontaneous ovulatory cycles or in IVF patients (Sterzik *et al.*, 1997, 2000). The etiology of numerous endometrial defects likely originates in the proliferative phase of the menstrual cycle, where a distinct ‘Proliferative Phase Defect’ has been described (Bromer *et al.*, 2009). The endometrium grows rapidly from menses until approximately cycle day 9 or 10, where endometrial growth slows despite rising estrogen levels and the absence of progesterone. The molecular determinants of this endometrial thickness set point are unknown at this time; however, several diseases associated with reduced implantation demonstrated reduced endometrial proliferative response. These include endometriosis and PCOS.

The ultrasonographic texture of the endometrium may have a prognostic value for implantation. In the proliferative phase, the endometrium has a hypoechogenic texture with a well-defined central line. This texture changes in the secretory phase, becoming hyperechogenic with no visualization of the central echogenic line. Significantly, higher pregnancy rates in the group with a mid-luteal phase homogenous hyperechogenic pattern were detected compared with a nonhomogenous pattern (Check *et al.*, 2003a, b).

Assessment of endometrial blood flow adds a physiological dimension to the anatomical ultrasound parameters and draws a lot of attention in recent years. Endometrial and subendometrial blood flows can now be objectively and reliably measured with 3D power Doppler ultrasound. Raine-Fenning *et al.* (2004b) showed that endometrial and subendometrial blood flows increased during the proliferative phase, peaking around 3 days prior to ovulation before decreasing to a nadir 5 days post-ovulation. In women with unexplained infertility, endometrial and subendometrial vascularity was significantly reduced during the mid-late follicular phase, irrespective of estradiol or progesterone concentrations and endometrial morphometry (Raine-Fenning *et al.*, 2004a). However, the use of endometrial and subendometrial blood flow in the prediction of implantation and pregnancy remains unclear (Ng *et al.*, 2007).

Transvaginal ultrasonography, especially when performed during the late follicular phase, provides excellent imaging of the uterus and of endometrial abnormalities. When hysteroscopy is considered to be the gold standard, the sensitivity, false-positive rate and positive predictive value were reported to be 99, 6 and 94%, respectively (Narayan and Goswamy, 1993). The positive predictive values for submucous fibroids and endometrial polyps were 92 and 91%, respectively (Narayan and Goswamy, 1993).

Saline infusion sonohysterography (SIS) is a procedure in which saline is instilled into the uterine cavity to provide enhanced endometrial visualization during transvaginal ultrasound. This technique improves detection of potential anatomic causes of reduced fertility, such as submucosal myomas, endometrial polyps and intrauterine adhesions. The sensitivity, specificity, positive predictive value and negative predictive value of SIS have been reported to be 98, 94, 95 and 98%, respectively (Ragni *et al.*, 2005). In addition, it helps avoid invasive diagnostic procedures as well as optimize the preoperative triage process for women requiring therapeutic intervention. It is typically scheduled early in the follicular phase of the menstrual cycle, after cessation of menstrual flow and before Day 10, as the endometrium is thin at this point in the cycle. Later in the cycle, focal contour irregularities of the endometrium may be mistaken for small polyps or focal areas of endometrial hyperplasia. Sonohysterography usually depicts leiomyomas and accurately assesses their location, size and degree of intramural extension. It has added advantage of better estimation of the percentage circumference projecting into the endometrial cavity. This is important because if removal is planned, a >50% projection of the leiomyoma into the uterine cavity suggests that hysteroscopic removal can be readily performed (Elsayes *et al.*, 2009).

Overall, even though ultrasound of the endometrium is easy to perform, and therefore, the imaging modality of choice in the detection of various endometrial pathologies, its prognostic value in determining pregnancy rate, is low.

Hysteroscopy is generally considered to be the gold standard in the diagnosis of intrauterine pathology, including endometrial polyp and submucous myoma. There is no doubt that hysteroscopy should be performed when there is suspicion of intrauterine pathology on transvaginal ultrasonography or SIS. Even when no abnormality is detected with these tools, subtle intrauterine pathologies have been noted in 18–50% of patients undergoing IVF when hysteroscopy is performed (Doldi *et al.*, 2005). However, the clinical significance of these findings is not sufficient to require hysteroscopic evaluation of all patients prior to IVF.

### Histological analysis of the endometrium

Noyes *et al.* (1975) examined the histological features of endometrial biopsies taken during 8000 spontaneous cycles in 300 women, and created the criteria for endometrial dating that previously accepted as gold standard approach for evaluating endometrial responsiveness and detecting endometrial abnormalities. However, a number of weaknesses in Noyes' approach have been identified. Dating is most accurate in the early and late luteal phase, but not in the implantation window, as very few histological parameters allow differentiation within the time span of the receptive endometrium (Myers *et al.*, 2004). This lack of objective measures likely led to the high intra- and interobserver variability noted. Intraobserver variability has been shown to be highest among infertile women during the implantation window (Murray *et al.*, 2004; Myers *et al.*, 2004). Furthermore, ovarian stimulation in artificial cycles may lead to differences in the timing of endometrial maturation compared with natural cycles (Papanikolaou *et al.*, 2005). Finally, in clinical trials, histological dating does not discriminate between women of fertile and infertile couples and is therefore not a valid tool in routine evaluation of infertility or implantation failure (Coutifaris *et al.*, 2004).

In addition to modifying the histological evaluation, the use of markers (such as  $\alpha_v\beta_3$  integrin, mucin I, LIF and *HoxA10*) has been investigated as a way to better assess endometrial development, and indirectly, endometrial receptivity. Although targeted disruption of several genes leads to an implantation defect, often the endometrial histology is normal, demonstrating the ability of a purely molecular defect to cause implantation failure. An Endometrial Function Test<sup>®</sup> (EFT) was developed that involves immunohistochemically staining of the endometrium with markers for the mitotic regulators cyclin E (the rate-limiting activator of the mitotic G1–S phase transition) and p27 (an inhibitor of cyclin E) (Dubowy *et al.*, 2003). However, the use of endometrial receptivity markers have not been widely adopted clinically because  $\alpha_v\beta_3$  integrin testing and EFT are the only commercially available methods, and their clinical use has not yet been definitively shown to improve pregnancy outcomes. There is however the high likelihood that molecular measures of endometrial receptivity will be more predictive than histology. Overall, there is still no perfect clinical assay to detect implantation defects.

### Currently available methods to improve implantation

Endometrial receptivity appears to be a major limiting factor in the establishment of pregnancy in number of gynecological diseases, and treatments to optimize implantation should be directed toward the underlying condition (Table 2).

The treatment of endometriosis is highly individualized and dependent on the desire for fertility or requirements for contraception. Medical treatment options for endometriosis include hormonal drugs such as combined oral contraceptives, progestogens, GnRH analogs or aromatase inhibitors. The aim of medical therapy is to prevent estrogen production or oppose its action. The role of medical therapies in infertility treatment has been reviewed, and there is little evidence to support their use in women with

**Table II Available methods to improve implantation in gynecological diseases.**

Gynecological disease	Therapy methods
Endometriosis	Excision or laser/diathermy ablation of endometriosis implants
Leiomyoma	Myomectomy
Hydrosalpinges	Salpingectomy Proximal tubal occlusion (if salpingectomy is technically difficult or not feasible)
Endometrial polyp	Hysteroscopic polypectomy
PCOS	Weight loss Insulin sensitizers
Adenomyosis	GnRH agonist treatment Surgical excision
Endometritis	Antibiotic therapy
Endometrial dysfunction due to ovarian stimulation	Cryopreservation of embryos Reduced ovarian stimulation

endometriosis who wish to conceive (Hughes *et al.*, 2007). One study suggests that long-term GnRH agonist treatment prior to IVF may improve implantation in women with endometriosis (Surrey *et al.*, 2002). The other option for treatment of endometriosis is to remove the lesions with laparoscopic excision or laser/diathermy ablation. A recent Cochrane review demonstrated a small improvement in clinical pregnancy rates with laparoscopic surgery when compared with diagnostic laparoscopy only (OR: 1.66; 95% CI 1.09–2.51) in patients with minimal and mild endometriosis (Jacobson *et al.*, 2010).

Leiomyomas that distort the uterine cavity, irrespective whether they are submucous or intramural, adversely affect fertility both spontaneous and during IVF treatment. The current management of myomas for fertility preservation or enhancement is surgical removal either by laparotomy, laparoscopy or hysteroscopy. The goals of myomectomy include: restoration of uterine morphology, return of normal menstrual function and enhancement of fertility. It is essential to use a precise surgical technique when performing a myomectomy so as not to adversely affect future fertility. Post-operative intrauterine balloon devices may be helpful in preventing adhesion formation. Given the global nature of the effect on endometrium, restoration of a normal uterine cavity without complete removal of the fibroid, may not fully alleviate the endometrial defect (Rackow and Taylor, 2010).

The preferred treatment method of endometrial polyps is polypectomy. Polypectomy can be performed blindly using a transcervical sharp curette; however, hysteroscopy-directed polypectomy using scissors, a loop electrode, electric probe or a morcellator is preferred to minimize damage to the surrounding endometrium and to ensure the polyp has been removed in its entirety. Operative resectoscopy with a loop electrode appears to be the technique of choice for endometrial polyps >2 cm or with a fundal location, whereas division of the polyp stalk using a bipolar electrode appears to be preferable for smaller, nonfundal polyps (Muzii *et al.*, 2007).

The treatment options for hydrosalpinges include drainage, salpingostomy, proximal tubal occlusion and salpingectomy. Laparoscopic salpingectomy should be considered for all women with bilateral hydrosalpinges prior to IVF treatment, as well as for a unilateral hydrosalpinx (Johnson *et al.*, 2010). Proximal tubal occlusion may be viewed as a valid alternative when salpingectomy is technically difficult or not feasible (Kontoravdis *et al.*, 2006).

Similarly, any inflammatory or infectious condition may alter endometrial receptivity (Weiss *et al.*, 2009). Several inflammatory cytokines impact endometrial development. Although there is no well-characterized assay to identify pelvic inflammatory conditions, they may be detected by elevated C-reactive protein, sedimentation rate or CA-125; however, all of these tests are nonspecific. Treatment should be directed toward eliminating the source of inflammation or infection.

While anovulation is an obvious cause of infertility in women with PCOS, emerging data suggest that endometrial receptivity may also contribute to infertility. Weight loss and insulin sensitizers have been shown to decrease circulating insulin and androgen levels, as well as improve reproductive performance (Taylor, 2000). However, further investigation is needed to determine precisely the mechanisms of insulin action in endometrial function and implantation to derive optimal therapies for women with PCOS in the treatment of infertility.

The association between adenomyosis and subfertility has been raised in a number of case series, and fertility was restored after the successful treatment of adenomyosis with multiple modalities, including GnRH agonist therapy (Grow and Filer, 1991; Hirata *et al.*, 1993), conservative surgical therapy via laparoscopy or exploratory laparotomy (Wood *et al.*, 1994; Wang *et al.*, 2006) and uterine artery embolization (Wood *et al.*, 1994; Wang *et al.*, 2006). However, the ability to improve implantation with surgical therapy of adenomyosis must still be investigated in well-designed clinical trials.

Idiopathic defects in endometrium can be caused by excessive ovarian stimulation (Macklon *et al.*, 2008). Options include cryopreservation and embryo transfer in a subsequent cycle in which aggressive stimulation is avoided. Alternatively, a second cycle can be performed with reduced ovarian stimulation and avoidance of unnecessary medication.

Interestingly, a number of studies demonstrated that local injury to endometrium by endometrial biopsy increases implantation and pregnancy rates in subsequent IVF–embryo transfer cycles (Barash *et al.*, 2003; Razieli *et al.*, 2007; Zhou *et al.*, 2008). There are several possible mechanisms by which endometrial sampling may increase its receptivity and improve the clinical pregnancy rate. Local injury to proliferative phase endometrium of IVF patients might induce decidualization of the endometrium and increase its implantation competency. Endometrial biopsy may also provoke wound healing, involving a massive secretion of different cytokines and growth factors, including LIF, IL-11 and heparin-binding epidermal growth factor-like growth factor, which are beneficial for the embryo implantation (Li and Hao, 2009). The injury may also recruit stem cells to the endometrium; adult stem cells have been shown to give rise to endometrium, perhaps creating a partially new endometrium free of epigenetic defects (Taylor, 2004; Du and Taylor, 2007).

Multiple other alternative treatment modalities have been studied. Systemic treatment with heparin and aspirin was performed to improve endometrial perfusion, prednisone to suppress fetal rejection, intravenous immunoglobulins to modulate endometrial immune cell function, recombinant LIF and progesterone to improve endometrial receptivity (Stephenson and Fluker, 2000; Stern *et al.*, 2003; Nosarka *et al.*, 2005; Pakkila *et al.*, 2005; Brinsden *et al.*, 2009). Unfortunately, with the exception of luteal phase support by progesterone administration in IVF, none of the treatments mentioned above were shown to be efficient in increasing implantation or pregnancy rates. Another attempted approach was to supplement embryo culture with putative adhesion promoting factors like hyaluronic acid or recombinant heparanase. Although the animal studies showed improved implantation rates, these results could not be translated to human (Simon *et al.*, 2003; Revel *et al.*, 2005).

## Conclusions and future prospects

Endometrial development resulting in endometrial receptivity during the window of implantation requires subtle collaboration of an extremely large number of different factors. Although many of them have been described, their individual function and role in the network of endometrial development is still not fully understood. Limitations in defining the role of individual molecules are multiple. Firstly, *in vivo* studies are performed in nonconception cycles, and cyclic expression of endometrial factors is thus unrelated to a subsequently ensuing

pregnancy. Secondly, gene suppression experiments in animals and *in vitro* culture systems in human provide only indirect evidence toward the function of relevant markers. Although our knowledge of endometrial receptivity is limited, it may still allow for significant improvement in the treatment of female infertility. As previously reviewed, suppressed expression or activity of certain protein and transcription factors can be responsible for infertility in unexplained infertility or in women with benign gynecological disorders. Therefore, the treatment approach could be to improve implantation by direct treatment of dysregulated endometrial proteins or transcription factors. Endometrial stem cells and gene therapy are promising options that can be effective in the future. Mice transfected with the *HOXA10* gene showed an increase in implantation sites, suggesting that augmentation of *HOXA10* expression by gene therapy can be a therapeutic option to improve implantation (Bagot *et al.*, 2000). In humans, primary endometrial epithelial cells and Ishikawa cells were successfully transfected by using liposome-mediated gene transfer (Charnock-Jones *et al.*, 1997; Bagot *et al.*, 2000). Moreover, successful gene transfection and expression in the intact human uterus was performed by transcervical administration of a lipoplex consisting of pcDNA3.1 plasmid containing the *Escherichia coli* lacZ reporter gene in perfused uteri at hysterectomy (Daftary and Taylor, 2001).

DNA methylation is an epigenetic modification of DNA. When promoter CpG islands become methylated, the associated gene typically becomes permanently silenced or repressed due to suppressed transcriptional activity. Decreased *HOX* gene expression secondary to hypermethylation of its promoter region is one of the proposed mechanisms of treatment resistance in endometriosis that can lead to an irreversible impairment in implantation. An approach using DNA demethylating agents to restore methylation aberrations can potentially have a role in the future treatment of endometriosis.

In summary, optimizing endometrial receptivity in fertility treatment will improve success rates. Evaluation of the implantation markers may help to predict pregnancy outcome and detect occult implantation deficiency. Manipulating the expression of key endometrial genes with medical, surgical or future cell and gene-based therapies may improve implantation rates. Current therapy relies on treating the underlying gynecological or medical disorders.

## Supplementary data

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

## Funding

NIH R01 HD036887 and U54 HD052668.

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