Defective endometrial receptivity

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The endometrium is one of the most fascinating tissues in the human body. Its sole purpose is to enable implantation of an embryo during a relatively short window of opportunity in the menstrual cycle. It is becoming clear that overcoming the current bottleneck in improvements to assisted reproductive techniques will require a closer look at the interface between uterus and embryo. Indeed, embryo implantation requires a cross talk with a receptive endometrium. Using sonography, hysteroscopy and endometrial biopsy we can learn about anatomical and functional markers of endometrial receptivity. This article reviews the factors which might cause defective endometrial receptivity. These include uterine polyps, septa, leiomyomata and adhesions. The effect of thin endometrium, endometriosis and hydrosalpinx is also described. Finally contemporary investigation of molecular markers of endometrial receptivity is described. Improving embryo implantation by a closer look inside the uterus is the key to increasing pregnancy rates in IVF. (Fertil Steril® 2012;97:1028–32. ©2012 by American Society for Reproductive Medicine.)

Key Words: Repeated implantation failure, RIF, in vitro fertilization, implantation, endometrial receptivity, endometrium, adhesion molecules

Successful implantation requires a receptive endometrium, a functional embryo at the blastocyst developmental stage and a synchronized dialogue between maternal and embryonic tissues (1). 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" (2). Endometrial development resulting in endometrial receptivity during the window of implantation requires the subtle collaboration of an extremely large number of different factors (3). Although our knowledge of endometrial receptivity is limited, it may still allow for significant improvement in the treatment of female infertility.

Uterine receptivity is defined as a restricted time-related period when the uterus is receptive to blastocyst attachment and implantation. The establishment of this endometrial transition, which supports embryo implantation, is primarily coordinated by ovarian hormones, estrogen and progesterone (4) which modulate uterine events in a spatiotemporal manner. Although numerous molecules involved in implantation have been identified in rodents and in humans, microarray analysis of the human receptive phase endometrium has only provided an insight into the role a select few molecules (5). The molecular mechanisms which regulate endometrial-blastocyst interaction remain poorly defined.

In order to exclude intrauterine factors that might impede embryo implantation, we perform office hysteroscopy prior to IVF. Diagnostic outpatient hysteroscopy performed using the vaginoscopic method can be easily carried out in almost all infertile patients, is well tolerated, takes just a few minutes and is highly informative.

INTRAUTERINE FINDINGS THAT COULD DECREASE EMBRYO IMPLANTATION

Polyps

The most common finding detected by office hysteroscopy is an intrauterine polyp. 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 (63 vs. 28%) (6). The practice guidelines of the AAGL recommend removing polyps in infertile women to improve fertility outcomes (7).

Septated and Sub-Septated Uterus

Among congenital Müllerian uterine abnormalities, the septate uterus is associated with the highest incidence of reproductive failure and obstetric complications, including first and second trimester recurrent miscarriage, premature delivery, malpresentation, intrauterine growth retardation (IUGR), and possibly infertility (8). Decreased vascular supply to the septum is proposed as the mechanism for lower fecundity. Nevertheless, the exact pathophysiology leading to reduced fertility is still unclear. Arcuate uteri, with an indentation of less than 1 cm, probably do not impact reproductive capacity.

Though septated and sub-septated uteri are amenable to simple hysteroscopic treatment, the role of metroplasty in patients with primary infertility remains controversial. There is controversy as to whether a septum should be removed prophylactically prior to a pregnancy or infertility

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treatment. Hysteroscopic incision of the septum has been shown to be a safe, simple, and efficient method of treating septate uteri (9). Evidence shows that, patients with an incomplete septum also benefit from hysteroscopic metroplasty (10). Surprisingly however, in a peer opinion poll, less than half of experts were in favor of surgery (11).

Hysteroscopic removal of the septum is commonly recommended because of its possible beneficial effect on fecundity and because of the potential benefits of reduced rates of miscarriage and preterm labor. Indeed, many IVF centers recommend removal of incomplete uterine septi before IVF to reduce the possibility of miscarriage and improve the pregnancy outcome (10, 12).

Leiomyomata

Fibroids have been noted to occur more frequently in women with infertility (13). Most women with fibroids are however fertile. Fibroids may interfere with fertility secondary to anatomical distortion and alterations to the uterine environment, with the effect determined largely by the location and size of the fibroid. In the setting of a distorted uterine cavity caused by leiomyomas, significantly lower IVF pregnancy rates were identified (14). There is limited molecular data to explain the mechanism behind these clinical observations. Recent studies demonstrate that leiomyomas may adversely affect the overlying endometrium and impair endometrial receptivity by altered expression of HOXA-10 in endometrial stromal cells during the window of implantation in 69% of patients with uterine leiomyomas (15).

With regards to IVF treatment, submucosal and intramural fibroids that protrude into the endometrial cavity have been associated with decreased pregnancy and implantation rates. Studies have shown that IVF outcome is markedly improved in women with cavity-distorting submucosal fibroids following myomectomy (16, 17). Recently, the presence of non-cavity-distorting intramural fibroids was also shown to be associated with adverse pregnancy outcomes in women undergoing IVF treatment (18).

Synechia-Asherman Syndrome

Intrauterine adhesions are secondary to endometrial trauma by curettage or cesarean section, with or without endometritis. Adhesions may involve layers of the endometrium, myometrium, or connective tissue. Adhesions derived from each of these tissues exhibit a characteristic hysteroscopic picture. Endometrial adhesions appear similar to the surrounding endometrium. Myofibrous adhesions, which are most commonly encountered, are characterized by the presence of a thin layer of overlying endometrium, the surface of which is furnished with many glandular ostia. The surface of connective tissue and fibrous adhesions lack an endometrial lining and contrast markedly with the adjacent endometrium. Infertility was observed in 802 out of 2151 (43%) patients with adhesions and depended on severity (19). Synechiae cause infertility by preventing sperm migration or embryo implantation. In order to evaluate adhesion extension and predict treatment success a scoring score can be used. The 1988 American Fertility Society scoring system for classification of intrauterine adhesions utilizes the menstrual history (normal, hypomenorrhea or amenorrhea) along with hysteroscopic and hysterosalpingographic findings (extent from less than one-third to greater than two-thrid and whether filmy or dense adhesions) (20). Treatment of Asherman syndrome aims to restore the size and shape of the uterine cavity, prevent adhesion recurrence, promote the repair and regeneration of the destroyed endometrium and restore normal reproductive function. Over the last century, many surgical techniques have been described (21). Hysteroscopy is the method of choice in the investigation and treatment of the condition. Before the use of hysteroscopy, the pregnancy rate after treatment was reported to be 51% (540 of 1052), which was only slightly better than found in those who had not been treated (133 of 292; 46%) (19). Women with Asherman syndrome who underwent hysteroscopic division of adhesion had increased conception rates (468 of 632; 74%). The use of postoperative intrauterine devices and balloons has been reported to prevent risk of adhesion recurrence (22). The management of moderate to severe disease still poses a challenge, and the prognosis of severe disease remains poor. Among those who conceived, the live birth per pregnancy achieved was 529 of 666 (79.4%). Women who conceive after treatment of Asherman syndrome still have a high risk of pregnancy complications, including spontaneous abortion, premature delivery, abnormal placentation, intrauterine growth restriction (IUGR), and uterine rupture during pregnancy or delivery (21). Repeat surgery may be necessary in some cases but may not always produce the desired outcome. Bone marrow derived cells that can regenerate endometrium (23) may be used for future treatment of severe Asherman syndrome. Future research should focus on the cellular and molecular aspects of endometrial tissue regeneration as well as the prevention of postsurgical adhesion formation and reformation.

THIN ENDOMETRIUM

It is generally accepted that no pregnancy does not occur when the endometrium measures <7 mm (24). Though routinely measured for more than two decades (25), it is now clear that implantation can sometimes occur despite a thin endometrium. Moreover, sonographic detection of average endometrial thickness is no guarantee for pregnancy, as it cannot quantify function. The thinnest peak endometrial thickness reported to support a viable fetus was 3.7 mm (26). Embryo implantation, clinical and ongoing pregnancy rates are significantly higher in patients with an endometrial thickness $>$9–10 mm (27–29). The target cross-section endometrial thickness is >7 mm, with a triple-line endometrial pattern, (24, 30, 31) whereas endometrial thickness <6 mm is associated with a decreased probability of achieving a full-term pregnancy. Advances in three-dimensional ultrasound, together with automated software for endometrial measurements, have resulted in more accurate and reproducible measures of endometrial volume which are less operator dependent than standard two-dimensional techniques. Endometrial volume was however not found to be a better predictor

of IVF outcome when compared to endometrial thickness measured on the day of hCG administration (32). More research is needed to determine clinical utility. It is not clear why a thinner endometrium leads to lower implantation rates. Casper hypothesized that high oxygen concentrations near the basal layer could lead to detrimental reactive oxygen species not present at the usual low oxygen tension of the surface endometrium (33).

ALTERED EXPRESSION OF ADHESIVE MOLECULES

Implantation involves a complex sequence of signaling events, resulting in the acquisition of adhesion ligands together with the loss of inhibitory components, which are crucial to the establishment of pregnancy. Histological evaluation, now considered to add little clinically significant information, should be replaced by functional assessment of endometrial receptivity. To date, a large number of molecular mediators have been identified, including adhesion molecules, cytokines, growth factors, and lipids (34). Endometrial biopsy samples can be used to identify molecules associated with uterine receptivity to obtain a better insight into human implantation (35). In addition, development of functional in vitro systems to study embryo–uterine interactions will lead to better understanding of the interactions existing between involved molecules. In order to increase implantation rates, an increase in our knowledge of the factors required for embryo implantation is vital (3). During the last few years we have been interested as to whether repeated IVF failure patients have a different gene profile during the window of implantation. We therefore performed global gene profiling of IVF patient endometrium, using high density oligonucleotide microarray technology, during the window of implantation for patients with RIF–IVF versus fertile controls. In addition, we have pursued validation of selected gene expression by quantitative real-time RT–PCR. These studies (24–26) have identified hundreds of differentially expressed genes that are potential markers. The challenge now is to identify accurate and reproducible biomarkers that could aid clinical identification of the implantation window.

Recently, we identified 13 miRNAs, differentially expressed in RIF endometrial samples that putatively regulate the expression of 3800 genes. Ten miRNAs were over expressed (including miR 145, 23b, and 99a) whereas three were under expressed (36). This suggests that RIF-associated miRNAs could be exploited as new candidates for diagnosis and treatment of embryo implantation failure. Future approaches to treating abnormal implantation may include direct modification of dysregulated endometrial proteins or transcription factors.

ENDOMETRIOSIS

Whereas some studies (37) fail to show decreased implantation rates in IVF patients with endometriosis, others (38) demonstrate significantly lower implantation rates with early as well as late stages of disease.

Infertility in endometriosis is thought mostly due to poor oocyte quality or aberrant embryogenesis, as IVF implantation rates are decreased if oocytes from donors with endometriosis are used (39). Nevertheless, decreased expression of implantation markers during the window of implantation (40, 41), may contribute to impaired implantation in endometriosis. About half of women with endometriosis do not express endometrial $\alpha_5\beta_3$ which correlates with the approximate 50% of patients with endometriosis who even with assisted reproductive technique cannot conceive (42). The mechanism for this aberration may be explained by altered methylation of HOXA10, a potent stimulator of $\alpha 5\beta 3$ expression, in women with endometriosis (42, 43). The decreased expression of biomarkers of implantation such as glycodelin A (GdA), osteopontin (OPN), lysophosphatidic acid receptor 3 (LPA3), and HOXA10 may indicate impaired endometrial receptivity in patients with endometriosis (44). This may provide an explanation for the pervasive infertility observed in some women with minimal pelvic endometriosis.

Another alteration observed in endometriosis relates to the steroid hormone pathways. Estrogen receptors (ER) are usually down regulated at the time of implantation. Women with endometriosis however were found to have an up regulation of ER (45). An increase in progesterone relative to estrogen must occur for successful endometrial receptivity. Progesterone resistance through the absence of the β isoform of its receptor is most likely due to aberrant methylation (46). These data suggest that reduced uterine receptivity may play a role in infertility associated with endometriosis.

HYDROSALPINX

Two meta-analyses have shown that women with hydrosalpinx have lower implantation rates (47, 48). One theory to explain the deleterious effect of a hydrosalpinx on the outcome of IVF is endometrial bathing with hydrosalpinx inflammatory fluid (49). The hydrosalpinx fluid may mechanically interfere with embryonic apposition or reduce endometrial receptivity. In the presence of hydrosalpinges, the expression of endometrial receptivity markers (e.g. a_vb_3 integrin) is reduced. Interestingly, two thirds of patients with hydrosalpinx who underwent salpingectomy demonstrated return of these markers back to normal levels (50). Moreover, a Cochrane review has demonstrated improved pregnancy rates with laparoscopic salpingectomy for hydrosalpinges prior to IVF (51). Whether hysteroscopic closure of hydrosalpinx using the Essure device yields similar results, has yet to be shown.

THE EFFECT OF GONADOTROPIC STIMULATION ON THE ENDOMETRIUM

The endometrium is controlled ultimately by the combined actions of estrogen and progesterone. The abnormal levels of these hormones during IVF treatment secondary to ovulation induction can affect the endometrial morphology and thereby perhaps endometrial receptivity (52, 53). In addition to histological changes, certain integrins expressed by the endometrium seem to be reduced in the glandular epithelium after ovulation induction. There may be an ideal estradiol level that should be reached during IVF treatment.

To have low estrogen levels may reduce the yield of oocytes, but high levels may impair the receptivity of the endometrium reducing integrin expression and leading to reduced implantation rates. A recent study has shown that the clinical pregnancy rates per transfer are significantly greater with cryopreserved embryos, than with fresh embryo transfers (54). This suggests a state of impaired endometrial receptivity is induced by ovarian stimulation, when compared with the artificial endometrial preparation required for frozen embryo transfer cycles.

TREATMENT TO CORRECT DEFECTIVE ENDOMETRIAL RECEPTIVITY

Endometrial receptivity now appears to be the bottleneck of the reproductive process. Basic and clinical research will help to improve understanding of the events of uterine preparation for embryo implantation. Microarray technology has broadened insight and has resulted in a number of gene expression analysis studies aimed at translating findings into clinical application (55). This knowledge could significantly improve the treatment of female infertility.

Treatment in animal models

As manipulation of human embryo implantation is complex, we and others have looked into animal models to study this interface. We have shown that supplementation of recombinant heparanase to the embryo culture medium before transfer into mouse uteri significantly increases implantation rates (56). Production of MMP2 increases in response to treatment with NO in rat, enabling tissue remodeling activity localized to the site of implantation (57). Research on embryo implantation in animal experiments is not necessarily transposable to the human model of implantation.

Ongoing human research

Reproductive surgery is the first step for the diagnosis and therapy of recurrent implantation failure in IVF. Possible anatomical malformations can be identified and treated via operative hysteroscopy (58). Endometrial biopsy samples can be used to identify molecules associated with uterine receptivity to obtain a better insight into human implantation. In addition, development of functional in vitro systems to study embryo–uterine interactions will lead to better understanding of the interactions between the molecules involved in this process. To date, only a few modalities have been employed to treat failures of embryo implantation. The knowledge acquired from this line of research could assist the development of specific therapeutics measures that will optimize embryo implantation. Barash and colleagues proposed that local injury to the endometrium may increase pregnancy rates (59). Further, priming of the uterus following endometrial cavity instillation using granulocyte colony-stimulating factor (60), human chorionic gonadotropin (hCG) (61), and piroxicam (62) before embryo transfer have been shown to improve pregnancy rates.

LOOK AT THE FUTURE

Endometrial-cell secretions poured into the uterine cavity are suitable for collection and analysis without the need for biopsy, and may provide important additional molecular information reflecting changes in endometrial physiology specific to a day of the cycle (63). If properly validated, the results would represent a step forward in the development of diagnostic tools to assess endometrial receptivity.

Novel in vivo approaches, including additives to the embryo culture or intrauterine flushing with putative adhesion promoting factors, could potentially increase implantation rates especially in repeated implantation failure.

In summary, many therapeutic options to treat endometrial dysfunction and thereby improve pregnancy rates have been tested. Endometrial gene therapy and local endometrial stimulation could be introduced in the future into the routine clinical setting.

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