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Disorders affecting endometrial receptivity

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ABSTRACT

Uterine receptivity is the ability of the endometrium to allow normal embryo implantation. Abnormal uterine receptivity leads to a range of reproductive problems, from infertility or defective implantation (miscarriage) to recurrent implantation failure after IVF procedures. The best management for our couples would be to identify in advance the possible disorders that could lead to implantation failure.

Most uterine malformations and acquired abnormalities of the uterine cavity are relevant to reproductive outcomes. However, the impact of some abnormalities remains controversial, such as adenomyosis and chronic endometritis.

External factors can also affect the receptivity of the endometrium, even if they are not located inside the uterine cavity. The possible effects of endometriosis, hydrosalpinx and obesity are factors to consider when considering assisted reproductive technology.

KEYWORDS

Endometrial receptivity, Müllerian malformations, chronic endometritis, adenomyosis, endometriosis, obesity.

MANUSCRIPT

Brief Introduction

Embryo transfer is the culmination and conclusion of in vitro fertilization (IVF). Once the embryo has been transferred, its future depends on its ability to implant, but also on the ability of the endometrium to host it. Therefore, the key to optimizing outcomes is to transfer an embryo of the highest possible quality, ideally euploid, to a suitably receptive uterus and endometrium. In this sense, the factors that determine the probability of implantation and pregnancy are dual: the quality of the embryo and the state of the uterus and endometrium.

The study of uterine receptivity involves aspects that are not exclusive but rather complementary; namely, morphology, functionality and synchronization of the endometrium with the embryo. All are key factors that indicate the global state of the endometrium and its receptivity, information that allows us to optimize reproductive results.

Recurrent implantation failure (RIF) refers to a scenario in which the transfer of optimal embryos fails with sufficient frequency to warrant further tests and/or interventions. This scenario can be avoided if disorders that lead to implantation failure are previously identified(1).

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In this chapter we will address the different conditions that can affect endometrial receptivity and reduce the chance of pregnancy.

1. Congenital uterine abnormalities – Müllerian malformations

Female genital malformations are deviations from a normal anatomy that occur during intrauterine development and in which the Müllerian ducts fail to form, canalize, fuse or absorb[2].

Mullerian malformations are associated with a significant decrease in implantation and pregnancy rates and an increase in miscarriage and preterm birth rates. The definition and significance of an arcuate uterus were a matter of debate for some time, in part due to a lack of consistency in classification. Both the ESHRE-ESGE and ASRM classification systems now consider this condition to be a minor anomaly[2,3].

In a prospective comparative study, reproductive outcomes, including clinical pregnancy, live birth, and preterm birth, were compared in women with a normal uterus and in those with a congenital uterine anomaly. A total of 2,375 women were included in the study, of whom 1943 (81.8%) had a normal uterus and 432 (18.2%) had a congenital uterine anomaly. Patients with an arcuate uterus presented similar clinical pregnancy rate (P = 0.78) and live birth rate (P = 0.91) to those with a normal uterus. However, women with major uterine anomalies presented statistically lower clinical pregnancy (P = 0.048) and live birth (P = 0.042) rates than controls. These results highlight the importance of accurate and reliable classification of uterine morphology prior to any assisted reproductive technique[4].

Transvaginal ultrasound is considered part of the fertility work-up, and objective documentation of abnormalities of the female genital tract is vital when evaluating infertile couples/individuals. 3D ultrasound is a non-invasive and safe method for the diagnosis and classification of Müllerian malformations. In fact, according to ESHRE guidelines, it is the "gold standard" test and should be supplemented by magnetic resonance imaging (MRI), Hysteroscopy (HSC) and Laparoscopy when a diagnosis is not completely clear. To date, no studies have evaluate whether 3D transvaginal ultrasound improves outcomes in patients with RIF; however, given the limited cost involved and its non-invasiveness, it would be logical to apply it as a routine diagnostic tool in the work-up of RIF, when available[1, 2].

Insofar as congenital uterine anomalies, good clinical practice guidelines indicate that surgical hysteroscopy should only be offered in the management of morphological malformations of the uterus if they are detrimental and can be resolved, such as uterine septal resection or metroplasty of T-shaped uterus[1, 2].

2. Acquired uterine anomalies

Assessment of the status of the endometrium and uterine cavity is an essential part of the initial evaluation infertile women or couples. Acquired intrauterine pathology is reported to be the cause of IVF failure in approximately 10-15% of patients. Indeed, some series describe a diagnosis of intrauterine pathology in up to 50% of women with RIF. Moreover, 85% of clinicians take anatomical and gynecological investigations into account when attempting to diagnose the cause of RIF[4, 5].

Hysteroscopy is the most accurate technique for diagnosing intrauterine or endometrial pathologies. In fact, in some cases, these pathologies cannot be detected by gynecological ultrasound. This has led several some professionals to include diagnostic hysteroscopy in the routine assessment of couples undergoing their first IVF attempt. There is evidence that performing hysteroscopy before IVF treatment significantly increases the probability of pregnancy in the subsequent IVF cycle of women with one or more failed IVF cycles. However, the importance of routine hysteroscopy prior to initiation of a first cycle of IVF has not been demonstrated. Diagnostic hysteroscopy to examine the uterine cavity should only be recommended in couples with a history of previous implantation failure, or when a uterine pathology has been detected by transvaginal ultrasound and further diagnosis is required. The purpose of this test is to exclude the existence of synechiae, Asherman's syndrome, submucous fibroids, endometrial polyps, adenomyosis and chronic endometritis[4,6].

Most acquired abnormalities of the uterine cavity are considered to be relevant to reproductive outcome and can be treated with well-established procedures such as endometrial polypectomy, surgical removal of submucous fibroids or intrauterine adhesions[4]. However, the impact of some abnormalities remains controversial.

Refractory or thin endometrium

The definition of a thin or refractory endometrium varies widely among authors, but is generally defined as an endometrium thickness of less than 7 or 8 mm on the day of human chorionic gonadotrophin injection in fresh IVF cycles or the day on which progesterone is initiated prior to frozen-thawed embryo transfer. In endometrial atrophy, which is considered the maximum expression of this pathology, there is a partial or complete absence of the functional endometrium.

In the past, research evaluating the effect of endometrial thickness on IVF outcomes was inconsistent. However, in recent years, large series have been published showing that clinical pregnancy rates and live birth rates decrease if embryo transfer is performed when endometrial thickness is below 7 mm. A retrospective cohort analysis of the Canadian database analyzed over 40,000 embryo transfer cycles and found that clinical pregnancy and live birth rates decreased ($P < 0.0001$) and pregnancy loss rates increased ($P = 0.01$) with each millimeter of reduction of endometrial thickness below 8 mm. In frozen-thawed embryo transfer cycles, clinical pregnancy ($P = 0.007$) and live birth rates ($P = 0.002$) decreased with each millimeter of decrease in endometrial thickness below 7 mm, with no significant difference observed in rates of pregnancy loss. The likelihood of achieving endometrial thickness ≥8 mm decreased with age[7].

Recent evidence endorses platelet-rich plasma (PRP) therapy as a promising treatment for patients with refractory endometrium[8].

Adenomyosis

Adenomyosis is defined as the presence of ectopic endometrial tissue (endometrial stroma and glands) within the myometrium, but it is not considered a form or subtype of endometriosis[9]. Given that adenomyosis can be associated with changes in the junctional zone close to the embryo implantation site, there may be a causal relationship between adenomyosis and subfertility. However, it is difficult to quantify the effect of adenomyosis on infertility and relevant data are limited. Infertility may arise in women with adenomyosis, mostly due to local endometrial inflammation, at least when lesions infiltrate the internal myometrium[10].

In contrast, numerous studies have attempted to determine the impact of adenomyosis on the reproductive outcomes of IVF. Benaglia et al. conducted a study in which women scheduled for IVF were prospectively screened for the presence of adenomyosis, and found that implantation rates were not affected in asymptomatic women diagnosed with adenomyosis. More recently, the results of systematic reviews suggest that adenomyosis has a negative effect on endometrial receptivity[10,11]. The effect of treatment for adenomyosis on pregnancy or live birth rates in women with RIF has not been evaluated[1]. Further research should aim to clarify the relationship between adenomyosis and infertility in order to refine treatment strategies.

Endometritis

Chronic endometritis (CE) is a controversial issue due to a complicated diagnosis and a lack of consensus on its impact on fertility. It is defined as persistent inflammation of the endometrial mucosa caused by bacterial pathogens, and is traditionally diagnosed by anatomopathology. To this end, an endometrial biopsy is required, ideally during a hysteroscopy, to identify plasma cells by hematoxylin and eosin staining or CD138-labelling. This method is nonspecific and may delay a definitive diagnosis, which will depend on the expertise of the pathologist in charge. Besides endometrial histology, macroscopic inspection of the uterine cavity via hysteroscopy is also employed to diagnose CE. The criteria for a positive diagnosis are the presence of mucosal oedema, focal or diffuse endometrial hyperemia and/or isolated or diffuse micropolyps. Some series have found concordance between hysteroscopic findings and histological diagnosis, though others have shown it to be as low as 20%. In fact, diagnosis by this technique can be complicated by the physiological changes that the endometrium undergoes during the cycle and should, therefore, be carried out by an experienced doctor during the initial proliferative phase of the menstrual cycle[12,13,14].

More recently, new molecular techniques have shown potential as tools for a reliable diagnosis of CE, such as next generation sequencing (NGS), but there are remain essential questions to be answered[14].

The limited data currently available suggest that CE evaluation is not necessary as part of the initial evaluation of infertile patients/couples, and women suffering from recurrent early pregnancy loss and RIF patients are likely to benefit most from screening and treatment of CE. ESHRE good practice recommendations for RIF include assessment of chronic endometritis (CE) and treatment with antibiotics in the case of a positive diagnosis[13, 15, 1].

Other studies have investigated adjuvant therapies as alternative treatment options, such as anti-inflammatory drugs, probiotics to regulate the female reproductive tract microbiome, and progestogens; however, there is not yet sufficient evidence to apply them in daily practice[16].

3. Communicating hydrosalpinx

Hydrosalpinx is defined as a distally occluded, dilated, fluid-filled Fallopian tube.

Tubal occlusion is a cause of infertility; in fact, the original indication for IVF treatments was a tubal pathology, assuming that pregnancy could be achieved by bypassing the damaged tube. However, the adverse effects of a hydrosalpinx persist even after IVF, and its negative effects on IVF outcomes are well documented. Many retrospective studies and some meta-analyses have highlighted a detrimental effect on implantation and pregnancy rates after fresh or cryopreserved-thawed embryos, and even after oocyte

donation. Moreover, there are several reports demonstrating an increased rate of spontaneous miscarriage[17, 18].

The negative effects of a hydrosalpinx have been attributed to different reasons. The strongest theory is that of a mechanical effect of hydrosalpinx fluid, whose leakage into the cavity can flush out the transferred embryo. A second theory, demonstrated in animal models, is based on the gametotoxicity of the hydrosalpinx fluid. Finally, it has also been suggested that the hydrosalpinx fluid is rich in cytokines and inflammatory response materials, which result in disordered and/or impaired endometrial receptivity[18].

Several studies have demonstrated that treatment of hydrosalpinx is mandatory if higher success rates are desired. Surgical interventions, such as salpingectomy, tubal occlusion or aspiration of hydrosalpinx fluid (if the patient is at high risk prior of surgery), should be considered in all women with hydrosalpinx who are due to undergo IVF treatment. In this context, the Cochrane review summarized the current evidence on the effectiveness of tubal surgery prior to IVF. Laparoscopic salpingectomy increased the odds of ongoing pregnancy and clinical pregnancy versus no treatment; to be specific, ongoing pregnancy rates in the intervention and control groups were 27-52% and 19%, respectively. Laparoscopic tubal occlusion in some studies increased clinical pregnancy rates, but there was very low-quality evidence that it is a reliable alternative to salpingectomy. Randomized controlled trials were needed to assess the effectiveness of other alternative treatments, such as ultrasound-guided aspiration. Unfortunately, none of the trials included reported live birth as an outcome, and no conclusions could be drawn about the adverse effects of interventions, as data on ectopic pregnancy, miscarriage, or surgical complications were not provided[19, 20].

Despite the fact that IVF outcomes are improved by salpingectomy when a hydrosalpinx is identified, some concerns have been raised about the potential negative effect of surgical intervention on ovarian function and vascularization. That said, current data suggest that salpingectomy does not compromise ovarian response to subsequent stimulation[19].

4. Endometriosis

Endometriosis is a highly prevalent chronic inflammatory disease defined as the presence of endometrium-like tissue outside the uterus. It affects about 10% of women of reproductive age and is one of the major causes of female infertility. It has a serious impact on quality of life due to the pain it provokes and the aforementioned reproductive problems[9].

Endometriosis is not completely understood, though the mechanisms involved in endometriosis-related infertility are known to be multifactorial and to include anatomical changes, reduction of ovarian reserve, endocrine abnormalities, genetic profile, immunity markers, inflammatory mediators, and altered endometrial receptivity[9].

The effect of chronic endometriosis on endometrial receptivity after IVF is undetermined due to a lack of relevant data, the main limitation being that factors associated with the disease are known to lead to lower implantation rates[15]. The effects of intrapelvic inflammatory processes (cytokines, growth factors, prostaglandins and reactive oxygen species, which are found in high levels in the peritoneal fluid) can interfere with ovulation, sperm function, gamete fertilization and embryo quality and migration. Assisted reproductive technology has been able to overcome some of these adverse phenomena, but they continue to have effects on oocyte and embryo quality[21].

When eutopic endometria from women with endometriosis are analyzed, several molecular aberrations can be observed, and it is hypothesized that these changes cause defects in endometrial receptivity. For example, levels of endometrial proteins that are essential for normal implantation are reported to be lower in patients with endometriosis, such as leukemia inhibitor factor, HOXA-10 and some cell adhesion molecules (called CAMs). In addition, inflammation is known to alter endometrial receptivity and has been specifically associated with endometriosis. Several immunological abnormalities, particularly those involving uterine natural killer cells, have been described in the endometrium of women with endometriosis[22, 23].

Garcia-Velasco et al. evaluated the expression of 238 specific genes directly related to endometrial receptivity by using the Endometrial Receptivity Array (ERA) to assess endometrial receptivity in patients with different stages of endometriosis and in healthy controls. No differences in gene expression were detected, suggesting that endometrial function is similar among women with and without endometriosis, and across the different stages of endometriosis[24].

Since implantation is a complex procedure in which the embryo is obviously a crucial factor, egg donation is the best way to rule out all the factors that can affect embryo implantation, apart from endometrial receptivity. Our group conducted a study in which healthy egg donors were shared out to 25 women with stage III-IV endometriosis and 33 healthy control women. There were no significant differences between the groups in pregnancy, implantation or miscarriage rates. Similarly, cumulative pregnancy rates in our oocyte donation program over a 10-year period were

similarly successful in women with a variety of reproductive disorders, including endometriosis[25, 26].

Clinical findings regarding donation support the idea that oocyte and embryo quality are the main determinants of IVF success, and seem to indicate that endometrial receptivity is similar in women with and without endometriosis. New prospective, randomized, and controlled studies are necessary to improve our knowledge of the enigmatic changes that occur in the uteruses of patients with endometriosis[25, 26].

5. Obesity and endometrial receptivity

Worldwide obesity has almost tripled in the last 50 years. Increased body mass index (BMI; kg/m2) is a major risk factor for many diseases, including cardiovascular disease, type II diabetes, musculoskeletal disorders, and some types of cancer. Furthermore, female obesity is considered to be a relevant risk factor for subfertility and infertility, with a significant reduction in implantation, pregnancy and live birth rates after IVF demonstrated in proportion to an increase in BMI[27,28,29].

Although most studies suggest that obesity does not significantly affect embryo quality, the role of BMI in oocyte and embryo quality cannot be ruled out[30,31,32].

In contrast, data regarding the detrimental effect of female obesity on endometrial receptivity are more consistent. In fact, studies using an oocyte donation model and including large patient samples have shown a reduction in implantation, pregnancy and live birth rates among obese recipients, demonstrating that outcomes are compromised even when embryo quality is good and suggesting a reduction in endometrial receptivity in obese women[33,34].

The mechanisms responsible for this detrimental receptivity are not well understood and constitute a hot topic for the field. Metwally et al. employed proteomic analysis to examine potential endometrial defects in obese and overweight women with recurrent miscarriage. Their studies described a negative correlation between endometrial glandular leukemia inhibitory factor (LIF) concentration and BMI, and endometrial protein profiles varied with an increased expression of haptoglobin in overweight/obese women[35,36].

On the other hand, systemic metabolism alterations induced by obesity are associated with impaired endometrial receptivity; for example, the disruption of insulin signaling has been closely related to endometrial dysfunction. Our group demonstrated that there is a linear increase in glycaemia, insulinemia, TSH, LDL cholesterol, triglycerides, and systolic and diastolic blood pressure and a reduction in HDL cholesterol in line with a rise in BMI[37,38]. We also designed a study in which we used endometrial receptivity analysis (ERA) to determine prospectively whether increased BMI affects endometrial receptivity by displacing the window of implantation (dWOI). We recruited a population of 170 infertile women with normal uteruses and no clinical history of recurrent miscarriage or implantation failure. These women were divided into four groups according to BMI. Endometrial receptivity assessed by ERA during a hormonally prepared cycle revealed that dWOI increased in a BMI-dependent manner. The pattern of displacement was generally delayed, as most of the endometria of the obese women were pre-receptive after 120 hours of progesterone administration. Such evidence allows us to conclude that metabolic disorders associated with obesity have a negative effect on endometrial receptivity, probably by delaying the dWOI[38].

6. Conclusions

Embryo implantation requires an adequate dialogue between a good quality embryo and a receptive endometrium. Implantation is still considered the enigma of reproductive medicine, and further research is needed to shed more light on the process.

The following conclusions can be highlighted (**Table 1**):

- The arcuate uterus does not appear to be associated with poor prognosis in ART.

- Surgical hysteroscopy should be offered to treat morphological uterine abnormalities that are major but can be resolved.

- If endometrial thickness is less than 7 mm on the day on which embryo transfer is scheduled, the patient should be advised that outcomes may be compromised. Nowadays, new therapies involving PRP are obtaining promising results.

- Some authors have suggested that adenomyosis can affect endometrial receptivity, though there is no consensus with respect to the matter.

- Chronic endometritis may be a detrimental factor for embryo implantation, but more studies are needed to standardize methods and the criteria for diagnosis, and to facilitate a consensus on treatment criteria and on the benefits of antibiotic therapy administered to improve reproductive outcome.

- When a hydrosalpinx is diagnosed prior to IVF, salpingectomy is the recommended approach.

- There is no evidence that endometriosis affects endometrial receptivity.

- Obesity has a negative effect on endometrial receptivity and can directly affect the endometrial

environment, leading to a delayed implantation window and, subsequently, worse ART outcomes.

Disorder	Management suggested
Arcuate uterus	No particular intervention
Major and reparable uterine malformations: - Class U1: Dysmorphic uterus - Class U2: Septate uterus	Surgical HSC: - Uterine septal resection - Metroplasty
Acquired intrauterine pathologies: - Endometrial polyp - Submucosal fibroids - Asherman's syndrome and synechiaes	Surgical HSC: - Polypectomy - Myomectomy - Adhesions resection
Refractory endometrium	PRP therapies is a prosing treatment
Adenomyosis affecting cavity	Hysteroscopic resection is suggested
Chronic endometritis	Antibiotic therapy
Hydrosalpinx	Salpingectomy by LPS
Endometriosis	No effect on implantation
Obesity	Diet and exercise for weight loss

HSC: hysteroscopy; **LPS**: Laparoscopy.

Table 1. Summary of conclusions on the management of disorders affecting endometrial receptivity.

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