

# Review- Role Of Endometrial Receptivity In IVF Success

Chaudhari Switi Ravindranath, Kaur Rajwinder, Kaur Dipneet, Kumar Sunil  
Department of Clinical Embryology & Reproductive Genetics,  
Rayat-Bahra University, Mohali, Kharar Punjab 140301

## ABSTRACT

*Endometrial receptivity plays a crucial role in the establishment of a healthy pregnancy in cycles of assisted reproduction. During IVF (in vitro fertilization), a proper endometrium thickness is one of the most difficult parameters to achieve and one of the most important prognostic factors of the success. This review article aims to elucidate the various factors that contribute to endometrial receptivity, including the hormonal regulation and molecular mechanisms that govern this process, as well as potential biomarkers for assessing endometrial receptivity. The factors affecting endometrial receptivity include: hormonal, genetic and immunological factors. During the receptive phase, different changes occur in endometrium (Cytoskeletal, biochemical and genetic). This review article discusses the interventions that can improve the uterine receptivity in Assisted Reproductive Technology (ART) cycles.*

**KEYWORDS-** Endometrial receptivity, Endometrium, IVF (in vitro fertilization), Assisted Reproductive Technology.

## INTRODUCTION

Endometrial receptivity is a state of an endometrium defined by its readiness for embryo implantation (Lessey and young, 2019). It is acquired through the series of events governed by the action of ovary-derived steroid hormones on their endometrial receptors converting the endometrium from a tissue unique in its ability to reject the embryo implantation to a tissue that enhances implantation (Rossman, 1940). The final stages are attained under the dominant control of progesterone capable of shifting an estrogen-primed, proliferative endometrium into secretory and of controlling the cascade of growth factors and cytokines essential for proper communication on the maternal-embryonic interface (Rashid *et al.*, 2011). However, the period in which endometrium provides an opportunity for an embryo to attach and implant, known as the window of implantation is time-limited and characterized by specific gene expression, morphologic and ultra-structural changes (Strowitzki *et al.*, 2006). Endometrial receptivity and implantation failure remains an unsolved enigma of the 20 million years of human life on our planet. Way of life, work or occupation, eating habits, relationship with partner, exposure to environmental toxins, physical activities etc., influence endocrine, psychological, immunological systems, changing the genome and influencing endometrial receptivity (Svetlana *et al.*, 2021). Endometrial receptivity is orchestrated by the central nervous system cortex, all endocrine glands and is regulated by estrogens, progesterone, other hormones, as well as autocrine and paracrine factors. Endometrial receptivity is the ability of the uterus to accept and develop a new embryo (Lessey, 2011). The reported many hormones (steroid and non-steroid) receptors, growth factors and cytokines required for implantation. Successful implantation requires coordination of embryo development and receptivity of the endometrium (Guzeloglu *et al.*, 2009).

## OBJECTIVES

Review and analyze the various factors affecting endometrial receptivity, including hormonal, genetic, immunological influences and role of endometrial receptivity in IVF success.

## STATEMENT OF PROBLEM

The establishment of a healthy pregnancy during cycles of assisted reproduction, such as IVF (in vitro fertilization), is critically dependent on endometrial receptivity. Achieving optimal endometrial thickness, a key prognostic factor for IVF success, remains a significant challenge. Despite advancements in reproductive medicine, the intricate hormonal, genetic, and immunological

factors that influence endometrial receptivity are not fully understood. Additionally, there is a need for reliable biomarkers to assess endometrial readiness and effective interventions to enhance uterine receptivity in ART cycles. This review aims to address these gaps by elucidating the hormonal regulation, molecular mechanisms, and potential biomarkers involved in endometrial receptivity, as well as discussing interventions that can improve outcomes in ART.

### HYPOTHESIS

The successful establishment of pregnancy in IVF cycles is significantly influenced by endometrial receptivity, which is governed by complex hormonal, genetic, and immunological factors. By comprehensively elucidating these factors and the associated molecular mechanisms, including cytoskeletal, biochemical, and genetic changes, it is possible to identify reliable biomarkers and effective interventions that enhance uterine receptivity, thereby improving the success rates of ART cycles.

### RESEARCH METHODOLOGY

Literature was reviewed by conducting a comprehensive search of relevant academic databases, including PubMed, MEDLINE, Embase, Scopus and Google scholar. Different specific keywords and phrases such as "endometrial receptivity," "IVF," "assisted reproduction," "endometrial thickness," "hormonal regulation," "molecular mechanisms," "biomarkers," "genetic factors," "immunological factors," "cytoskeletal changes," "biochemical changes," "ART interventions." were used to find the related research. Summarize the findings from selected studies to elucidate the various factors influencing endometrial receptivity and the effectiveness of different interventions.

### ENDOMETRIAL INFERTILITY

It is estimated that 10% of couples worldwide suffer from infertility. One third are due to male factors, one third due to female factors and one third due to a combination of both. ART, including in vitro fertilization (IVF), has come to help some of the affected, but far from all. In IVF, focus has been on optimizing production of high-quality embryos and the issue of implantation has been less addressed (Achache and Revel, 2006). Endometrial receptivity is the endometrium's capability to let an embryo implant. In a normal menstrual cycle, the endometrium reaches the receptive state around 6 to 9 days after the LH peak (The *et al.*, 2016). Only during this very limited time frame are the conditions optimal to allow embryo implantation. This is interesting considering that other tissues (i.e. fallopian tube or peritoneum) allow implantation in a more uncontrolled fashion. The purpose of the tight regulation of endometrial receptivity can be partly explained by the fact that the endometrium during the receptive phase is also able to assess embryo quality (Achache and Revel, 2006). It therefore serves not only as the receiver and growing ground for embryos but can also expel embryos unlikely to succeed. This has been shown in vitro where endometrial stromal cells could be shown to migrate towards healthy embryos whereas migration was inhibited by low quality embryos (Weimar *et al.*, 2012). It is however considered that endometrial factor infertility and implantation issues pose a significant challenge to overcome in ART and that more research is needed to define different types of endometrial receptivity disturbances (Furukawa *et al.*, 2007).

#### **Endometrial receptivity disturbances:**

**1) Recurrent implantation failure:** RIF is a condition in IVF where implantation and pregnancy fails to occur despite measurable and controllable factors being seemingly optimized. It is usually defined as three or more failed embryo transfers with good quality embryos (Simon and Laufer, 2012). Causes of recurrent implantation failure: Gamete/embryo factors, Oocyte quality, Sperm quality, Parental chromosomal anomalies, Uterine factors.

**2) Asherman's syndrome:** Asherman's syndrome is an endometrial pathological condition that presents with intrauterine adhesions and scarring. It can be caused by irradiation, surgical trauma, infection or be idiopathic and can lead to amenorrhea, dysmenorrhea, repeated pregnancy loss and infertility. The predominant treatment option is removal of adhesions through hysteroscopy, but adhesions often recur and the endometrium remains unresponsive and thin (Yu *et al.*, 2008). This implies that the pathophysiology of Asherman's syndrome is closely linked to the processes of endometrial regeneration with impaired tissue regeneration leading to scarring (Queckborner *et al.*, 2019).

**3) Endometriosis:** Endometriosis is the most perplexing gynecological condition (Xu *et al.*, 2015). Endometriosis influences 10%-15% of all reproductive-age females and 70% of women with persistent pelvic pain (Parasar *et al.*, 2017). Endometriotic lesions can also develop in other places including the fallopian tube, abdominal wall, bowels, cervix, bladder, and vagina (Farland *et al.*, 2017). Endometriosis is a female reproductive system disorder where the endometrium-like tissue develops outside of the uterus; it usually affects the ovaries and peritoneum, causing premenstrual discomfort and dysmenorrhea (Eisenberg *et al.*, 2018).

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Several studies from the IVF setting have also failed to show impaired implantation in endometriosis after exclusion of confounding factors. Thus far, the question whether endometriosis significantly impairs endometrial receptivity is still very much under debate (Diaz *et al.*, 2000; Simon *et al.*, 1994).

### **Factors affecting endometrial receptivity:**

The establishment of endometrial receptivity is critically dependent on hormonal regulation. The menstrual cycle, governed by the hypothalamic pituitary ovarian axis, orchestrates cyclic changes in the endometrium in response to fluctuations in estrogen and progesterone levels (Kao *et al.*, 2002). Progesterone is essential during the secretory phase of the menstrual cycle to establish and maintain endometrial receptivity. Disruptions in hormonal balance, as observed in PCOS, can interfere with endometrial receptivity and impede implantation (Lessey, 1998). The pathophysiology of pregnancy failure associated with dys-regulated signaling pathways is multi-factorial and complex. It involves various factors, such as immune dysfunction, endocrine imbalances, genetic abnormalities, and environmental factors. Therefore, further research is needed to fully understand the mechanisms involved in pregnancy failure and develop effective interventions to prevent it (Sherwin *et al.*, 2007; Critchley *et al.*, 2001).

**Hormonal factors:** The effect of progesterone on the endometrium is essential for implantation. This hormone causes down-regulation of estrogen receptors and the onset of decidualization in the endometrium. Estradiol levels also determine the endometrial thickness. LH gonadotropin also increases in the pre-implantation stage (Norwitz *et al.* 2001).

**Genetic factors:** Many genetic factors are likely to be involved in the success or failure of implantation. The endometrial signature of genes during the window of implantation provides the opportunity to design diagnostic screening tests for patients with infertility and endometrial disorders and for targeted drug discovery for treating implantation based infertility (Cao and Tulac, 2002). Genetic defects are the causes of 80% of first-trimester abortions. Many genetic factors play a role in implantation success or failure. In general, the expression of these unique genes during the implantation window allows diagnostic tests to design, find, and treat the implantation failure uses (Neykova *et al.* 2020).

**Immunological factors:** A variety of immune cells increase in the secretory phase. The uterine natural killer cells (uNKs) and macrophages are in this category.

**Cytoskeletal changes:** Integrin family is expressed in the receptive endometrium and plays an important role in implantation (Stenhouse *et al.*, 2019).

### **Why is ART cycles receptivity not achieved optimally?**

The endometrium is the final barrier to pregnancy in ART. One of the physiological factors involved in receptivity is progesterone, which leads to completion of proliferation of luminal epithelium and its differentiation toward the secretory phase (Proliferation and differentiation switching) (Ombelet *et al.*, 2008). A small estradiol surge with high progesterone initiates the embryo-uterine communication (Mascarenhas *et al.*, 2012). Therefore, estradiol and progesterone signals cause uterine receptivity in regular cycles, but in ART cycles, these hormones are replaced by different Controlled ovarian hyper-stimulation protocols (COH protocols) (Cha *et al.*, 2012). During these cycles, the estradiol levels are much higher than the physiological limit (Norwitz *et al.*, 2001).

### **This review article discusses the interventions that can improve the uterine receptivity in ART cycles :-**

**1) PRP (Platelet-rich plasma)** Plasma platelet concentrate is obtained by centrifuging blood. Platelets are non-nucleated cell fragments derived from the bone marrow megakaryocytes. Platelet granules are rich in proteins, growth factors, and cytokines. When an injury occurs, the platelets are activated and secrete these molecules, which play an important role in the wound healing process. Platelet products also play an important role in endometrial remodeling as well as embryo-maternal crosstalk at the time of implantation (Furukawa *et al.*, 2007). Endometrial cell growth after intrauterine treatment with PRP is a special treatment for thin endometrium patients during ART cycles. In infertile women in FET cycles, it can increase the endometrial vascularity (Tandulwadkar *et al.*, 2017). Mechanisms that cause endometrial regeneration include increased cell migration and proliferation of various cell types, as well as the expression of matrix proteins (Aghajanova *et al.*, 2018). The advantages of PRP include easy access, low price, and a rich source of growth factors. Because PRP is autologous, it is not toxic. There are four types of platelet concentrate available based on the classification.

P.PRP (pure platelet-rich plasma)

L.PRP (leucocyte and platelet-rich plasma)

P.PRF (pure platelet-rich fibrin)

L.PRF (leucocyte and platelet-rich fibrin).

2) **Endometrial Scratching:** Endometrial scratching (ES) is the intentional injury to the endometrium using instruments, most frequently a Pipelle catheter inserted through the uterus. This is a simple method that causes mild damage and has been proposed to improve pregnancy outcomes in assisted reproductive technology (ART) (Nastri *et al.*, 2012). As the demand for assisted reproductive technology continues to increase, so does the pressure to improve success rates of in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI)/Intrauterine Insemination (IUI). It is essential to determine strategies to enhance embryo implantation for all women undergoing ART.

3) **Acupuncture:** Acupuncture is an ancient Chinese medicine that has a history of two thousand years. The use of acupuncture in reproductive endocrinology and infertility is common worldwide (Stankiewicz, Smith *et al.* 2007). Acupuncture in the lower limbs and lower abdomen can increase the blood flow to the ovaries and uterus and ultimately the endometrium (which is one of the characteristics of endometrial receptivity).

4) **Pharmacological treatments:** Aspirin is a Non-steroidal anti-inflammatory drug (NSAID). It has been reported that a low dose of aspirin can increase the pregnancy rate by increasing the uterine receptivity in patients undergoing IVF cycles (Gelbaya *et al.*, 2007).

5) **Nutritional supplements:** Carnitines (including L-carnitine and acetyl L-carnitine) are water-soluble vitamins essential for mitochondria's metabolism to produce energy and protect DNA from the oxidative stress. The addition of carnitine to the culture medium was associated with increased oocyte quality, embryo maturation and development (Carrillo-González and Maldonado-Estrada 2020). In sub-fertile women with PCOS, taking carnitine oral supplements improves the biomarkers of oxidative stress; decreases the lipid peroxidation and body mass index (BMI); improves the glycemic control; and increases the ovulation rate uterine thickness and pregnancy rate (Ismail *et al.*, 2014).

6) **Endometrial receptivity assay (ERA):** The Endometrial Receptivity Array (ERA) is a pioneering test developed in 2009 after more than 10 years of research. ERA is designed to evaluate endometrial receptivity and determine the ideal time for embryo transfer.

### **How is it done?**

ERA is only done in medicated frozen embryo transfers (FET) at Lister. You will have endometrium prepared with oestrogen and progesterone exactly the same way as for a medicated FET cycle. On the day an embryo would normally be transferred, you would have endometrial biopsy instead. It is very similar to an embryo transfer procedure which you would have previously had. However, in contrast to the transfer (where we do not want to disturb the lining) we will be gently moving the instrument within the uterus for a few seconds and take a biopsy.

### **Impact of endometrial receptivity on fertility outcomes**

The success of embryo implantation and subsequent pregnancy depends on endometrial receptivity (Lessey, 2000). The complex interplay of molecular events between the developing embryo and the endometrium is integral to embryo implantation. Optimal endometrial conditions are necessary for successful embryo implantation, and any abnormalities in endometrial receptivity can result in implantation failure and infertility (Singh *et al.*, 2011). Hormonal regulation of endometrial receptivity is a crucial factor that plays a critical role in establishing a receptive endometrial environment (Brosens *et al.*, 2002). Estrogen and progesterone levels in the endometrium are necessary for preparing the endometrium for embryo implantation. Inadequate levels of these hormones have been reported to cause implantation failure and infertility in several studies (Evans and Salamonsen, 2013). The establishment of a receptive endometrial environment is dependent on molecular mechanisms that are involved in endometrial receptivity. These mechanisms govern gene expression, cytokine signaling, and extracellular matrix remodeling, and their dysregulation can result in impaired endometrial receptivity and implantation failure (Horcajadas *et al.*, 2008). To determine the optimal timing for embryo transfer, it is crucial to assess biomarkers of endometrial receptivity (Miravet *et al.*, 2015). Various biomarkers that can be used to predict endometrial receptivity have been identified, such as the measurement of endometrial thickness, uterine artery blood flow, and the expression of certain genes and proteins. These biomarkers can improve the accuracy of embryo transfer timing and increase the success rates of ARTs (Haouzi *et al.*, 2010). The clinical implications of assessing endometrial receptivity in ART have been extensively researched, and multiple studies have reported a significant enhancement in pregnancy rates through endometrial receptivity assessment (Miravet *et al.*, 2015; Horcajadas *et al.*, 2008). Utilizing biomarkers to predict endometrial receptivity has been demonstrated to enhance embryo transfer success rates and decrease the incidence of implantation failure (Haouzi *et al.*, 2010).

### ANALYSIS

After review of various papers, Fertility depends upon the various factors which increase the endometrial receptivity and the invasive and non-invasive tests along with some ayurvedic medications in affordable prices.

### SUMMARY

To summarize, the establishment of endometrial receptivity is a crucial stage in achieving a successful pregnancy, involving a complex interplay of hormonal, molecular, and cellular mechanisms. The molecular mechanisms underlying endometrial receptivity entail intricate interactions between the embryo and the endometrium, which entail the secretion of numerous signaling molecules by the embryo, and the expression of a set of genes and proteins by the endometrium. Consequently, comprehending the factors that regulate endometrial receptivity is critical to enhance the success rates of ARTs and develop new therapies for infertility. Endometrial receptivity is influenced by several factors, including hormonal regulation, molecular mechanisms, and endometrial receptivity biomarkers. Hormonal imbalances, such as those observed in PCOS, can interfere with the process of endometrial receptivity and result in implantation failure. Endometrial pathologies, such as endometriosis and polyps, can also impact endometrial receptivity and lead to pregnancy complications. Furthermore, systemic conditions, including obesity and diabetes, can negatively impact endometrial receptivity. Therefore, a comprehensive understanding of the mechanisms that control endometrial receptivity is necessary to optimize the chances of successful implantation and pregnancy.

### CONCLUSION

This review article presented different interventions that might improve endometrial receptivity in ART cycles. PRP has growth factor and anti-inflammatory properties. It is safe and it has positive effects on endometrial receptivity. Endometrial scratching may be associated with the secretion of growth factors and cytokines involved in the wound healing process and may also contribute to enhancing the embryo implantation. Acupuncture is effective as a complimentary medicine and should be used along with routine medical approaches. Medications like aspirin, growth hormone and heparin that are used in ART cycles improve the receptivity. Use of stem cells in human is limited and although they have positive effects on animals, they have a long way to be safe enough to be used for human. Nutritional supplements like Carnitines, vitamin E and melatonin seems to be safe and effective in endometrial receptivity. Endometrial receptivity assay (ERA) was introduced as an accurate molecular tool to determine the endometrial receptivity status. Future studies will have to focus on molecular cell biology and physiology of the endometrium.

### RECOMMENDATION

After review of all papers it is recommended that before embryo transfer make sure that endometrial receptivity is achieved.

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