Sys Rev Pharm 2021;12(3):54-67
A multifaceted review journal in the field of pharmacy

Endometrial Receptivity In Art Cycles: A Review On Different Aspects Of Improvement

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ABSTRACT
Background: 65% of the causes of infertility are related to female factors. Receptive endometrium is essential for a successful pregnancy. In ART cycles, receptivity is not achieved optimally.
Main body: Uterine receptivity is the ability of the uterus to accept a competent blastocyst. 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 ART cycles.
Conclusion: 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. In FET cycles, developmental synchrony between the embryo and uterus is maintained. Endometrial receptivity assay (ERA) was introduced as an accurate molecular tool to determine the endometrial receptivity status.

Keywords: Infertility, endometrial receptivity, assisted reproductive technology, embryo implantation

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BACKGROUND

Infertility is the absence of a clinical pregnancy despite 12 months of unprotected and regular intercourse. 65% of the causes of infertility are due to female factors, the most common of which are increasing maternal age, fallopian tubes infection damage, polycystic ovary syndrome (PCOS), endometriosis, anatomical damage or congenital structural defects in the reproductive organs, decreased ovarian reserve or disorder of the hypothalamic-pituitary-ovarian axis. 20 to 50% of the causes of infertility are due to male factors. Some of the most common causes include structural problems in the sperm, decreased sperm motility, diseases that increase oxidative stress such as varicocele, and childhood febrile diseases such as mumps. However, 15 to 30% of infertility cases remain unexplained. Recurrent pregnancy loss (RIF) is a defect in fecundity and childbearing. However, it does not fit into the classic definition of infertility. The infertility rate among couples is approximately 10-30%, which causes the patients to endure ART cycles (La Marca and Mastellari 2020).

Embryo quality and receptive endometrium are essential for a successful pregnancy. Physiologically, there are three stages in embryo implantation: embryo apposition, embryo attachment, and invasion, which involve molecular connections between the embryo and the receptive endometrium. During the first two stages, the trophoblast attaches to the endometrial receptor. This stage continues with the blastocyst invasion and penetration into the epithelial lamina on day 20 to 24 of the menstrual cycle, called the implantation window (Cha, Sun et al. 2012).

Main text

The endometrium is the covering layer that covers the inner surface of the uterus. The uterine endometrium responds strongly to estrogen and progesterone hormones. Under the influence of estrogen (follicular stage), it will be thicken; under the influence of progesterone, its mucosal glands become larger (secretory phase). The endometrium consists of two layers: the basal layer, which always remains without changes at different uterine endometrial development stages and functional tissue that changes during the menstrual cycle and regenerates by the underlying layers after shedding in menstrual bleeding (Kurita and Terakawa 2020).

Uterine receptivity is the ability of the uterus to accept a competent blastocyst. The factors affecting endometrial receptivity include:

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, Schust et al. 2001).

Genetic factors

Genetic defects are the causes of 80% of first-trimester abortions. Many genetic factors play a role in implantation success or failure. For example, expression of the HOXA10 gene in the endometrium increases at the time of implantation. The USAG1 gene is also involved in endometrial receptivity. The expression of the EBAF gene in the secretory phase can prepare the endometrium for implantation. In general, the expression of these unique genes during the implantation window allows diagnostic tests to design, find, and treat the implantation failure causes (Neykova, Tosto 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. UNKs lack cytotoxic properties and act as sources for the secretion of cytokines essential for implantation (such as Vascular endothelial growth factor (VEGF)). These cells are also involved in accepting semi-allogeneic embryo and preventing the rejection of the embryo. The secretion of cytokines and chemokines such as Granulocyte-macrophage colony-stimulating factor (GM-CSF) and Leukemia inhibitory factor (LIF) increases by endometrial cells, essential for implantation (Hannan, Evans et al. 2011). All of these factors play a role in the natural endometrium receptivity and its preparation for implantation. Defects in any of these stages can lead to pregnancy failure in more than 75% of cases. Factors that pathologically affect the uterine receptivity include mechanical factors (like congenital or acquired), congenital septa, fibroids, polyps, adhesions and inflammatory factors that include endometriosis, adenomyosis, hydrosalpinx and endometritis (Ahn, Singh et al. 2017). During the receptive phase, the endometrium undergoes morphological, cytoskeletal, biochemical, and genetic changes. After ovulation, an increase in superficial stromal edema is seen by day 21. Stromal cells near the spiral arteries show an increase in the cytoplasm volume (decidualization) that lasts until day 25. This transformation is mesenchymal to epithelial transformation. Edema increases the thickness of the endometrium and there are also changes in the length and torsion of the spiral arteries. The mitotic activity in the glandular epithelium, endoplasmic reticulum, and glycogenic vacuoles also increased. The population of uterine leukocytes $CD16^+$ / $CD56^-$, which plays an essential role in maternal allorecognition of embryo trophoblasts, is also increased (Quinn and Casper 2009).

Cytoskeletal changes

Integrin family is expressed in the receptive endometrium and plays an important role in implantation (Stenhouse, Hogg et al. 2019). More specifically, $\alpha 4\beta$ and $\alpha 5\beta 1$ integrin are proposed as endometrial molecular markers that bind to the fibronectin ligand in the trophoblast cells. The rapid increase in estradiol causes the clustering of integrins and their binding activity to bind to the ligand (Qu, Zhang et al. 2015).

Biochemical and genetic changes

HOXA10 plays an important role in genetic control and embryo development in the female reproductive tract. HOXA10 controls downstream genes that lead to endometrial development and endometrial receptivity. This gene is controlled by progesterone in a dose-dependent manner (Zhu, Sun et al. 2013). Heparin-binding EGF-like growth factor (HB.EGF) is part of the EGF family, expressed in the human uterus at the time of implantation and controlled by steroids. The transmembrane part is also associated with cell adhesion and migration, allowing contact with the blastocyst and acting as a chemoattractant (Lessey, Gui et al. 2002).

LIF is also part of the family of cytokines that control the proliferation, differentiation, and cell survival (Margioula-Siarkou, Prapas et al. 2017). LIF induces the expression of cytokines and other regulatory molecules and plays a vital role in embryo implantation (Suman, Malhotra et al. 2013). It is also the essential cytokine affecting the endometrial receptivity, which is expressed in glandular epithelial cells during window of implantation (WOI) under the influence of progesterone (Díaz-Gimeno, Ruiz-Alonso et al. 2013).

MiRNAs are small, single-stranded sequences that do not encode proteins. They are between 18-25 nucleotides that play an essential role in Post Transcriptional Modification (PTM) and gene expression (Guzeloglu-Kayisli, Kayisli et al. 2009). Due to their stability in biological fluids, they are used as biomarkers to measure the receptivity (Shukla, Singh et al. 2011). The miRNome profile of the endometrial tissues during the implantation window can predict the pregnancy outcome. Specific miRNAs are associated with the endometrial receptivity status (miR-455-3p and miR-4423-3p) (Drissennek, Baron et al. 2020).

Markers and predictors of receptivity

One of the endometrium receptivity markers is tissue markers, including the appearance of uterine pinopods visible under an electron microscope. Pinopods are the cytoplasmic projections of the luminal epithelial cells that increase in WOI and augment the blastocyst adhesion (Quinn and Casper 2009). Under the influence of estrogen and progesterone, the glandular epithelium and stroma express the genes essential for endometrial receptivity and blastocyst adhesion (Cha, Sun et al. 2012). Another predictor of receptivity in ART cycles is the endometrial thickness and endometrial volume. In one study, the incidence of pregnancy was almost three times higher when the endometrial thickness was more than 12 mm (Kehila, Kebaili et al. 2010). Other studies have reported thicknesses greater than 14 mm at the time of human chorionic gonadotropin (HCG) injection (Corbacioğlu and Baysal 2009). However, some authors believe that endometrial volume is a stronger predictor for endometrial receptivity. Volumes greater than two mL indicate a positive predictor of ART results (Kovachev, Ganchev et al. 2005). The endometrial pattern on ultrasound can also be a predictor of endometrial receptivity. These patterns are either homogeneous or multi-layered in their echogenic form. Studies reveal that pregnant women show a multi-layered pattern at the time of oocyte retrieval (Yang, Zhang et al. 2018).

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, Cooke et al. 2008). A small estradiol surge with high progesterone initiates the embryo-uterine communication (Mascarenhas, Flaxman 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, Sun et al. 2012). During these cycles, the estradiol levels are much higher than the physiological limit (Norwitz, Schust et al. 2001). This amount of estradiol can cause structural changes in the endometrium. Excessive changes in LH surge also increase pre-ovulatory progesterone secretion, which can lead to premature endometrial secretory changes that disrupt the implantation process. In such cases, WOI starts earlier, and even with a good quality embryo transfer, the implantation rate will be low. Changes in the ratio of estrogen to progesterone, the concentration of growth factors, and the profile of adhesion molecules induced by COH protocols can also have different effects on the endometrial receptivity. During COH protocol, endothelial pinopods' expression occurs earlier, causing a shift in the implantation window time (Egashira and Hirota 2013). This review article discusses the interventions that can improve the uterine receptivity in ART cycles.

PRP (Platelet-rich plasma)

Plasma platelet concentrate is obtained by centrifuging blood. Platelets are non-nucleated cell fragments derived from the bone marrow megakaryocytes. The cytoplasm of the platelets is divided into two categories: chromomere which contains the accumulation of granules, and agranular hyalomere which is rich in cytoskeletal proteins (Grozovsky, Giannini et al. 2015). 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. Platelets are also involved in inflammatory processes and produce immunomodulation factors such as CD40 soluble ligand CD154, which play an essential role in innate and adaptive immunity crosstalk (Yung, Fu et al. 2017).

Platelet products are classified based on the percentage of constituents. However, the most common types are Pure PRP and Leukocyte PRP. Both products are made by centrifuging the whole blood with anticoagulants and adding platelet activators such as calcium or thrombin before consumption (Bos-Mikich, de Oliveira et al. 2018). After PRP administration, the expression of IL1.β, IL6, and IL8, which plays an important role in inflammatory responses, decreased (Marini, Perrini et al. 2016).

Other studies on cows indicated that PRP-treated cells showed higher proliferation rates and higher expression of genes involved in implantation. The progesterone receptor expression was higher in these samples, and the researchers claimed that PRP treatment could be effective in treating endometriosis (Aghajanova, Houshdaran et al. 2018).

Sato et al. performed the first PRP studies on humans. The researchers found that the platelets replaced the endothelium and muscle layer, remodeled the spiral arteries, and dilated them, which ultimately provided adequate blood flow in the placenta's intervillous space (Sato, Fujiwara et al. 2005). Subsequent studies have shown that blood platelets act as regulators of neovascularization and luteinization in tissue remodeling during the corpus luteum formation process. Platelet products also play an important role in endometrial remodeling as well as embryo-maternal crosstalk at the time of implantation (Furukawa, Fujiwara et al. 2007).

Endometrial cell growth after intrauterine treatment with PRP is a special treatment for thin endometrium patients during ART cycles. Intrauterine infusion of PRP promotes neoangiogenesis. In infertile women in FET cycles, it can increase the endometrial vascularity (Tandulwadkar, Naralkar 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, Houshdaran 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) (Dohan Ehrenfest, Rasmusson et al. 2009).

In summary, the function of growth factors within PRP is as follows:

-These growth factors increase neutrophil infiltration and macrophages, which stimulate angiogenesis, fibroplasia, and matrix deposition, and ultimately leads to tissue regeneration.

-These growth factors have anti-inflammatory properties.

Another PRP role is in cases of repeated implantation failure (RIF) that is the lack of gestational sac formation in the ultrasound view in the fifth week of pregnancy or the absence of pregnancy after three high-quality embryo transfer or no pregnancy despite having ten or more embryos in different cycles (Coksuer, Akdemir et al. 2019). PRP with cytokines and growth factors such as Platelet-derived growth factor(PDGF), Fibroblast growth factor (FGF), Vascular endothelial growth factor (VEGF), Epidermal growth factor (EGF), Insulin-like growth factor 1 and 2 (IGF-1, IGF-2) ,Transforming growth factor(TGF), Hepatocyte growth factor (HGF), connective tissue growth factor (CTGF), and IL8 can improve the uterine thickness (Oh, Kim et al. 2015). Many researchers cite uterine expression of IGF-1 during implantation as a marker of endometrial receptivity (Zhou, Shen et al. 2020).

In cases where inflammation is the cause of decreased endometrial receptivity, PRP plays a role in healing, renewal, and regeneration (Amable, Carias et al. 2013). Coagulation factors, proteins with antimicrobial and fungicidal properties, can indirectly affect the production of interleukins and chemokines and control inflammation symptoms. On the other hand, dense granule derived factors such as adenosine diphosphate, adenosine triphosphate, serotonin, histamine, dopamine, and calcium ions can play a key role in the process of tissue homeostasis and repair (Pochini, Antonioli et al. 2016).Intrauterine injection of PRP can reduce local inflammatory responses by reducing polymorph nuclear neutrophils and inhibiting fluid retention in the uterine lumen (Sfakianoudis, Simopoulou et al. 2019). Growth factors in PRP also correct the thin endometrial thickness. PRP can alter gene expression in the endometrium and improve receptivity conditions. In one study, c-myc gene expression regulates in PRP-treated endometrial cells. c-myc which is involved in cell proliferation and activation by EGF is a component of PRP The expression of pro-inflammatory factors such as prostaglandin, IL1β, and nitric oxide is also reduced (Marini, Perrini et al. 2016).

PRP can up-regulate LIF expression in endometrial stromal cells. LIF plays an important role in endometrial receptivity and embryo attachment (Salehnia, Fayazi et al. 2017). PRP may enhance trophoblast placentation (Kim, Shin et al. 2019). However, the preparation of PRP is not well standardized; therefore, platelet content and growth factors are not well determined. The greatest biological effect is when the platelet concentration is almost 1,000,000 per microliter. Concentrations with fewer platelets have suboptimal biological effects, and higher concentrations may have inhibitory effects (Weibrich, Hansen et al. 2004).

Endometrial Scratching

Endometrial scratching before the embryo transfer is a technique to increase the implantation rate. Endometrial biopsy in the luteal phase was associated with an increased pregnancy rate after IVF (Gibreel, Badawy et al. 2013). Endometrial scratching may be associated with the secretion of growth factors and cytokines involved in the wound healing process and may also contribute to embryo implantation. The increased chance of implantation is due to the enhancement of decidualization induced by endometrial scratching (Günther, von Otte et al. 2020).

Another hypothesis is increased synchrony between the endometrium and the transmitted embryo. Thus, endometrial scratching, if performed in the pre-embryo transfer cycle, can balance the maturation and overgrowth of the endometrium caused by COH regimes during ART (Narvekar, Gupta et al. 2010). Secretion of cytokines, interleukins, and growth factors, migration of macrophages and dendritic cells that repair the damaged endometrium can play a positive role in embryo implantation .Accumulation of macrophages and neutrophils is associated with VEGF and Interferon secretion, and VEGF increases the vascularization of the decidua (Wheeler, Jena et al. 2018).

VEGF is also a regulator for angiogenesis, which ultimately increases the uterine perfusion and endometrial thickness, both of which play an important role in endometrial receptivity. Because mid-luteal VEGF levels decrease in women with unexplained infertility, endometrial scratching in these women can increase the endometrial receptivity and improve IVF outcome (Liang, Han et al. 2015).Endometrial scratching is an inexpensive and straightforward method to correct the asynchrony between the endometrium and the embryo stage, due to the wound healing process through the local secretion of pro-inflammatory cytokines such as macrophage inflammatory protein-1E,Tumor necrosis factor (TNFα), osteopontin, IL, growth factors, and dendritic cells which stimulate implantation. Angiogenesis following endometrial injury is a significant factor in the secretion of cytokines and growth factor and NK cells that increase the tissue blood flow and prevent embryo rejection (Wadhwa and Mishra 2018).

Since the wound healing mechanism requires the passage of time, endometrial scratching in the luteal phase is associated with the highest rate of pregnancy in the next cycle. This effect may persist for a long time due to the presence of monocytes at the wound site (Vitagliano, Andrisani et al. 2019).

In one study, endometrial scratching on days 21-26 of the luteal phase resulted in a clinical pregnancy rate three times higher than the control group in the next cycle (Gui, Xu et al. 2019). Some researchers believe that double endometrial scratching can be helpful. Narvekar et al. performed endometrial scratching twice, once on days 24-25 of the previous cycle and again on days 7-10 of the next cycle, which made the clinical pregnancy rate triple compared to the control group (Narvekar, Gupta et al. 2010). On the other hand, some researchers state that endometrial scratching on the day of ovulation can reduce successful IVF chances (Karimzade, Oskouian et al. 2010).

A study showed that endometrial scratching did not significantly differentiate the clinical pregnancy rate (CPR) and live birth rate (LBR) in women who enter the ART cycle (van Hoogenhuijze, Kasius et al. 2019). Endometrial scratching (ES) also has destructive effects on the receptive endometrium and embryo implantation on the day of ovulation. However, ES may increase CPR and LBR in women with the failure of two or more Fresh IVF ETs (Karimzade, Oskouian et al. 2010).

The results of a study conducted in Egypt in 2019 on women with unexplained infertility showed that the clinical pregnancy rate was higher in the group that underwent endometrial biopsy than the control group. The results of this study showed that endometrial scratching in the first cycle increases the CPR. However, low to moderate pain and bleeding were more common in this group (Maged, Rashwan et al. 2018). Endometrial scratching is also associated with acceptable results in women with unexplained infertility undergoing IUI (Gupta, Radhakrishnan et al. 2018).

After a decade of endometrial scratching procedures and more than 50 Randomized controlled trial (RCTs) to determine the effect of ES on pregnancy outcomes, the results are still contradictory. Although observations indicate the usefulness of ES in women with previous ET failure , precise information on the benefits of this method on women experiencing the first embryo transfer cycle is not available (Mahran, Ibrahim et al. 2016).

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) (Guo, Wang et al. 2011). A 2019 study showed that acupuncture might affect the expression of has-miR 345-3p and has-miR 3135b, triggering a cascade of endocytosis, axon guidance, oxytocin signaling, HIPPO pathway, and estrogen signaling and ultimately increases the endometrial receptivity (Mu, Li et al. 2020).

Acupuncture is the second treatment used by infertile couples in the united Kingdome (UK). It has a positive effect on the menstrual cycle and uterine electromyography and enhances the endometrial receptivity by improving the endometrial morphology, and augmenting the uterine microcirculation, progesterone receptor regulation, and α7β3 integrin regulation, LIF, VEGF and HOX A10 (Zhong, Zeng et al. 2019). A study showed that acupuncture increases the pregnancy rate by increasing the volume of the uterine blood flow (Zhang, Gao et al. 2014).

Acupuncture is a safe and non-invasive method that has few side effects. A review study conducted in 2019 found that most studies performed acupuncture 30 minutes a day or every other day. In studies in which acupuncture was used as adjunctive therapy in addition to medical treatment, endometrial thickness was significantly increased. However, in most studies, if this intervention was used alone, it did not significantly change the endometrial thickness (Gu, Zhang et al. 2019).

A review study conducted in 2019 showed that acupuncture in women with a low and poor ovarian reserve and those who present with RIF had the best result. Indeed, acupuncture is used as a complementary treatment in the IVF cycle (Shuai, Li et al. 2019). Positive results of acupuncture in IVF were observed in women whose previous several IVF cycles had failed (Schwarze, Ceroni et al. 2018).

This might be due to the effect of acupuncture on improving the embryo quality (Xie, Peng et al. 2019), increasing the endometrial receptivity (Zhong, Zeng et al. 2019), and reducing anxiety and depression (Sator-Katzenschlager, Wölfler et al. 2006). However, the exact mechanism of these effects needs further studies. In traditional acupuncture, the patient's skin is pierced with multiple needles, causing irritation, bleeding, and pain. The new Trans Cutaneous Electrical Acupoint Stimulation (TEAS) method is a non-invasive acupuncture method that can enhance reproducibility with electro-acupuncture in the same way as acupuncture (Zheng, Feng et al. 2015). In others, acupuncture has been used during ET and some during COH to increase the ovarian response to COH protocols increase the uterine receptivity , and increase the embryo quality (Wei, Liu et al. 2020).

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, Kyrgiou et al. 2007). The daily dose of aspirin changes the balance from thromboxane A2 to prostacyclin, thereby causing vasodilation and increased blood flow (Rubinstein, Marazzi et al. 1999). A low dose of aspirin increases the ovarian function and response by improving the ovarian and uterine perfusion and is associated with optimal results in IVF/ICSI pregnancy rates. Aspirin can also increase the number of oocytes taken in ART cycles, thereby increasing pregnancy chances (Gizzo, Capuzzo et al. 2014).

Clinical use of growth hormone in infertility is related to women with low ovarian reserve, poor response, low oocyte quality, and maternal aging (Homburg, Singh et al. 2012). The growth hormone affects the quality of the oocytes and the receptiveness of the endometrium and increases the implantation potential by improving the thickness of the endometrium (Drakopoulos, Pluchino et al. 2016). Growth hormone treatment protocols in ART cycles increase serum estradiol, IGF-1 and VEGF and enhance arcuate vascular perfusion in the endometrium (Liu, Wu et al. 2020).

Endometrial receptivity can be achieved by the exogenous use of estradiol and progesterone by various regimens. Estradiol induces endometrial proliferation and induction of progesterone receptors. On the other hand, progesterone, by acting on these receptors, initiates luteinization and causes the endometrium to enter the implantation stage (Paulson 2011).

Low molecular weight heparin prevents the occurrence of thrombosis at the embryo site. Heparin promotes the expression of adhesion molecules, the most important of which are the selectin and cadherin families which are essential for implantation (Massimiani, Lacconi et al. 2019). HB-EGF is a member of the EGF family that promotes growth and differentiation and is a potent mitogen that acts as a chemoattractant for a group of cells and accumulates in the trophoblast area, increasing the attachment of the blastocyst to the endometrium (Chobotova, Spyropoulou et al. 2002).

Vitamin E, as a powerful antioxidant, dilates the uterine arteries and helps the blood vessels to expand. The endometrial glands also increase after consumption of this vitamin E, and with this mechanism, it improves endometrial receptivity (Takasaki, Tamura et al. 2009).

Progenitor stem cells

Endometrial progenitor cells:

Endometrial Mesenchymal Stem Cells (eMSC) play an important role in endometrial regeneration during the menstrual cycle and prepare the uterus for pregnancy. This cell group is multipotent and phenotypically similar to MSCs of the bone marrow and adipose tissue. They can also form colonies and differentiate into other cells. This group of cells has specific CD markers 44, 73, 29, 105, and 90 (Tempest, Maclean et al. 2018). Several studies show that uterine stem cell expresses the markers of uterine receptivity. One of these markers is noggin and HOXA11 (Du, Yuan et al. 2016). Rac1, which is essential for eMSC migration and movement, is also expressed at the implantation site (Grewal, Carver et al. 2008). Integrins, which are also used as markers of endometrial receptivity, are expressed by these cells (Spitzer, Rojas et al. 2012).

In cases where this cell population in the endometrium is reduced, it can lead to infertility and recurrent miscarriage. Drug approaches that increase the population of endometrial progenitors can increase the loss of endometrium thickness and lead to cell regeneration and increase the pregnancy rate. RIF, for example, is associated with the loss of the eMSC population. Dpp4 inhibitor, oral sitagliptin 100 mg daily for three cycles, can cause homing and engraftment of the uterine stem cells in the damaged tissue (Tewary, Lucas et al. 2020). Also, the use of eMSC obtained from the endometrial tissue or menstrual blood alone or in combination with PRP in RIF's patients can increase the endometrial thickness (kochar kaur, Allahbadia et al. 2020)

Bone marrow stem cells:

BMSCs grafts on the uterine stroma after ischemia or trauma had been done. Their mechanism of action is the production of trophic factors to maintain the cells. Bone marrow-derived Hematopoietic stem cells (HSCs) provide a niche for hematopoiesis and aid in developing and maintaining the sinusoidal network. Bone marrow derived MSCs also help regenerate the endometrium (Nelson and Roy 2016). A study showed that injection of BMSCs into the uterus of rats with low endometrial thickness increased its thickness, and expression of cytokines, vimentin, integrin, and LIF, which are markers of endometrial receptivity (Zhao, Zhang et al. 2015).

Umbilical cord MSC:

Mesenchymal stem cells are derived from different sources (it is better to use less invasive types including umbilical cord MSC). MSCs of the Umbilical cord (UC-MSCs) regenerate the endometrial cells, collagen remodeling, cell proliferation and epithelial recovery, and induce the expression of the alpha estrogen and the progesterone receptor (Xin, Lin et al. 2019) .Exosomes released from ucMSC increase the cell viability and decrease the cell death (Wang, Hu et al. 2020). The results of a study showed that ucMSC could increase the endometrial thickness due to the secretion of growth factors rather than differentiation into functional cells (Rungsiwiwut, Virutamasen et al.). ucMSC with a collagen scaffold increases the endometrial glands and expression of the vimentin gene (Benor, Gay et al. 2020).

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 carnitineas 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, Hamed et al. 2014). In women with RIF, the addition of 3mg/day L-carnitine with estradiol valerate was associated with increased markers of uterine receptivity, uterine thickness, and increased pregnancy, implantation, and live birth rates (Edris and Barakat 2018).

Vitamin E increases the thickness of the endometrium, the growth of uterine glandular epithelium and blood vessels, and the expression of VEGF protein (Eftekhar, Tabibnejad et al. 2018). The uterine microenvironment responds to circadian rhythms, thus responding to physiological functions (Pan, Taylor et al. 2020). Melatonin is secreted rhythmically from the pineal gland in darkness and accounts for regulation of the biological clock. Melatonin enhances the ovulation and embryo implantation (Fernando, Wallace et al. 2018). It can also protect the endometrial cells from apoptosis and oxidative stress Melatonin receptors 1A and 1B are expressed on the surface of the human endometrium. Therefore, treatment with melatonin every 12 hours until the 6th day of gestation can increase the progesterone's secretion, which facilitates the decidualization process by acting on these receptors. Also, by increasing the secretion of P53, it causes the secretion of LIF, which enhances the implantation process (Chuffa, Lupi et al. 2019). Melatonin increases the uterine receptivity by increasing the development of the corpus luteum before pregnancy. The results of a study show that if melatonin is used 14 days before mating in mice, it will reduce the secretion of the estradiol hormone and increase LIF's secretion, thus enhancing implantation (Guan, Xie et al. 2017).

Frozen Embryo Transfer (FET)

One of the destructive effects of ovarian hyper-stimulation protocols is a decrease in the uterine receptivity in the same cycle. Increasing progesterone on the day of HCG injection in fresh cycles reduces the chance of pregnancy. More specifically, women with a progesterone level between 0.8- 1.1 ng/ml are less likely to have a successful pregnancy than those with a progesterone level of less than 0.8 ng (Venetis, Kolibianakis et al. 2013). Because ovulation stimulation protocols are not performed at the cycle of embryo transfer in FET cycles, this developmental synchrony between the embryo and the endometrium is maintained and leads to the uterine receptivity, so the chance of pregnancy increases (Wong, Mastenbroek et al. 2014).

Endometrial receptivity assay (ERA)

Personalized medicine is a well-accepted phenomenon in reproductive medicine. Each patient should be examined and treated separately. Therefore, setting a special routine day for all patients for embryo transfer is not suitable (Nisal, Diwekar et al. 2020). The ERA test helps assess each patient's endometrial condition individually and determine the appropriate embryo transfer day for the same person. Hence, it is called personalized embryo transfer. Endometrial receptivity assay (ERA) was introduced as an accurate molecular tool to determine the endometrial receptivity status. Endometrial Receptivity Array (ERA) is a diagnostic molecular test based on microarray technology that, based on the expression of 238 genes in endometrial biopsy specimens, divides it into three categories: receptive, non-receptive, and proliferative (Díaz-Gimeno, Horcajadas et al. 2011).

The ERA determines the best embryo transfer time for each woman by determining the transcriptome profile of 238 genes expressed at different stages of the endometrial cycle (Messaoudi, El Kasmi et al. 2019). This method is used for patients who are under 37 years old and have at least three or more failed pregnancies despite the good quality embryo transfer (at least two or more times for older women) (Tan, Kan et al. 2018). Studies conducted on the uterine receptivity with histological dating and ERA suggest that using the ERA method for endometrial dating is much more accurate (Díaz-Gimeno, Ruiz-Alonso et al. 2013).

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 most of the studies claim it has positive effects on endometrial receptivity and enhances the pregnancy rate in ART cycles. According to the hypothesis, endometrial scratching may be associated with the secretion of growth factors and cytokines involved in the wound healing process and may also contribute to embryo implantation. There is controversy in the results of studies. It seems that more studies should be carried out to define the exact effect of this procedure in ART successfulness. Acupuncture is a safe and non-invasive method that has few side effects. Most studies declare that 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 receptivity and has good results in enhancing the pregnancy rate. 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. Umbilical MSC and Endometrial MSC are tried in human and the results show positive effects on the endometrial receptivity. Nutritional supplements like Carnitines, vitamin E and melatonin seems to be safe and effective in endometrial receptivity. In FET cycles, developmental synchrony between the embryo and uterus is maintained, and ovulation stimulation protocols are not performed; all these factors increase the uterine receptivity, thus increasing the chance of pregnancy. Endometrial receptivity assay (ERA) was introduced as an accurate molecular tool to determine the endometrial receptivity status. Studies show that it is a useful molecular tool to personalize the embryo transfer day and enhance the chance of pregnancy. Summary of the drugs and other interventions to enhance endometrium receptivity shown in Table 1 and Table 2.

Abbreviations

ART: assisted reproductive technology, **PCO**: polycystic ovary syndrome, **RIF**: recurrent pregnancy loss, **uNKs**: uterine natural killer cells, **VEGF**: vascular endothelial growth factor, **GM-CSF**: granulocyte-macrophage colony-stimulating factor, **LIF**: leukemia inhibitory factor, **HB.EGF**: heparin-binding EGF-like growth factor, **PTM**: post transcriptional modification, **WOI**: window of implantation, **HCG**: human chorionic gonadotropin, **LH**: luteinizing hormone, **COH**: controlled ovarian hyper-stimulation protocols, **PRP**: platelet rich plasma, **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, **PDGF**: platelet-derived growth factor, **FGF**: fibroblast growth factor ,**EGF**: epidermal growth factor, **IGF-1, IGF-2**: insulin-like growth factor 1 and 2 ,**TGF**: transforming growth factor, **HGF**: hepatocyte growth factor, **CTGF**: connective tissue growth factor, **IVF**: in vitro fertilization, **TNF**: tumor necrosis factor, **ES:** endometrial scratching, **IUI**: intra uterine insemination, **CPR**: clinical pregnancy rate, **LBR**: live birth rate, **RCT**; randomized controlled trial, **UK**: united Kingdome, **TEAS**: trans Cutaneous Electrical Acupoint Stimulation, **NSAID**: non-steroidal anti-inflammatory drug, **eMSC**: endometrial, **ICSI**: intra cytoplasmic sperm injection, **BMSCs**: bone marrow stem cells, **HSCs**: hematopoietic stem cells, **UC-MSCs**: umbilical cord Mesenchymal Stem Cells, **FET**: frozen embryo transfer, **BMI**: body mass index, **ERA**: endometrial receptivity assay.

Declarations

Ethics approval and consent to participate: Not applicable
Consent for publication: Not applicable
Availability of data and material: Not applicable
Competing interests: The authors declare that they have no competing interests.
Funding: Not applicable
Authors' contributions: BR wrote the article. SB edited and made the final revision. All authors read and approved the final manuscript.

ACKNOWLEDGEMENTS

The authors would like to thank Shiraz University of Medical Sciences, Shiraz, Iran and also Center for Development of Clinical Research of Nemazee Hospital and Dr. Nasrin Shokrpour for editorial assistance.

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Table 1: Summery of the drugs used for increasing endometrial receptivity.

Drug	**Cases**	**Results**
Transdermal estrogen and oral aspirin	human	Increased receptor markers (integrin and laminin) in uterine tissue, pregnancy rate, uterine blood flow (Chi, He et al. 2018).
Low dose of aspirin	human	Increase the pregnancy rate by increasing the uterine receptivity in patients undergoing IVF cycles (Gelbaya, Kyrgiou et al. 2007).
	mice	Increased implantation rate and pregnancy rate, ovarian response, integrin expression and LIF (Zhao, Chang et al. 2010).
	human	Improves ovarian responsiveness, uterine and ovarian blood flow velocity, implantation, and pregnancy rates in patients undergoing in vitro fertilization (Rubinstein, Marazzi et al. 1999).
	human	Increased uterine thickness, uterine receptivity (Wang, Kang et al. 2020).
	human	Increase the number of oocytes taken in ART cycles (Gizzo, Capuzzo et al. 2014).
Growth hormone	human	Increased egg retrieval and number of transferable embryos, improved endometrial ultrasound pattern, increased implantation and pregnancy rate (Lan, Lin et al. 2019).
	human	Affects the quality of the oocytes and the receptiveness of the endometrium and increases the implantation potential by improving the thickness of the endometrium (Drakopoulos, Pluchino et al. 2016).
	human	Increase serum estradiol, IGF-1 and VEGF and enhance arcuate vascular perfusion in the endometrium (Liu, Wu et al. 2020).
17 beta estradiol and heparin	rat	Increased endometrial repair and kisspeptin in the ERK1 / 2 P38 pathway resulting in estrogen entry into endometrial tissue and increased uterine thickness. Decreased apoptosis (Zhang, Xu et al. 2020).
Heparin	human	Increase serum estradiol, IGF-1 and VEGF and enhance arcuate vascular perfusion in the endometrium (Massimiani, Lacconi et al. 2019).
G-CSF	human	Increased uterine thickness, implantation and pregnancy rate, decreased premature abortion rate (Jain, Mahey et al. 2018).

HB-EGF	human	Increasing the attachment of the blastocyst to the endometrium (Chobotova, Spyropoulou et al. 2002).
Vitamin E	human	Increase the endometrium thickness (Morsy, Sabri et al. 2020).
	human	Dilates the uterine arteries and helps the blood vessels to expand. The endometrial glands also increase after consumption of this vitamin E, and with this mechanism, it improves endometrial receptivity (Takasaki, Tamura et al. 2009).
	human	Increases the thickness of the endometrium, the growth of uterine glandular epithelium and blood vessels, and the expression of VEGF protein (Eftekhar, Tabibnejad et al. 2018).
Melatonin	human	Increase pregnancy rate (Mokhtari, Akbari Asbagh et al. 2019).
	human	Melatonin every 12 hours until the 6th day of gestation can increase the progesterone's secretion, which facilitates the decidualization process by acting on these receptors. Also, by increasing the secretion of P53, it causes the secretion of LIF, which enhances the implantation process (Chuffa, Lupi et al. 2019).
Carnitine	human	Increased oocyte quality, embryo maturation and development (Carrillo-González and Maldonado-Estrada 2020).
Carnitine oral supplements	human	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, Hamed et al. 2014).
L-carnitine with estradiol valerate	human	Increased markers of uterine receptivity, uterine thickness, and increased pregnancy, implantation, and live birth rates (Edris and Barakat 2018).

Table2: Summery of nondrug treatments to enhance endometrium receptivity.

treatment	**case**	**results**
PRP	human	PRP improves intrauterine receptivity and embryo implantation (Frantz, Ferreira et al. 2020).
	human	Improvement of endometrial thickness and higher pregnancy rates (Agarwal, Mettler et al. 2020).
	human	Produce immunomodulation factors such as CD40 soluble ligand CD154, which play an essential role in innate and adaptive immunity crosstalk (Yung, Fu et al. 2017).
	human	The expression of IL1.β, IL6, and IL8, which plays an important role in inflammatory responses, decreased (Marini, Perrini et al. 2016).
	human	Higher proliferation rates and higher expression of genes involved in implantation. The progesterone receptor expression was higher in these samples, and the researchers claimed that PRP treatment could be effective in treating endometriosis (Aghajanova, Houshdaran et al. 2018).
	human	Replaced the endothelium and muscle layer, remodeled the spiral arteries, and dilated them, which ultimately provided adequate blood flow in the placenta's intervillous space (Sato, Fujiwara et al. 2005).
	human	Play an important role in endometrial remodeling as well as embryo-maternal crosstalk at the time of implantation (Furukawa, Fujiwara et al. 2007).
	human	Intrauterine infusion of PRP promotes neoangiogenesis. In infertile women in FET cycles, it can increase the endometrial vascularity (Tandulwadkar, Naralkar et al. 2017).
	Human	Increased cell migration and proliferation of various cell types, as well as the expression of matrix proteins (Aghajanova, Houshdaran et al. 2018).
	human	Uterine expression of IGF-1 during implantation as a marker of endometrial receptivity (Zhou, Shen et al. 2020).

	human	PRP can up-regulate LIF expression in endometrial stromal cells. LIF plays an important role in endometrial receptivity and embryo attachment (Salehnia, Fayazi et al. 2017).
	human	PRP may enhance trophoblast placentation (Kim, Shin et al. 2019).
	human	PRP with cytokines and growth factors such as Platelet-derived growth factor (PDGF), Fibroblast growth factor (FGF), Vascular endothelial growth factor (VEGF), Epidermal growth factor (EGF), Insulinlike growth factor 1 and 2 (IGF-1, IGF-2) ,Transforming growth factor(TGF), Hepatocyte growth factor (HGF), connective tissue growth factor (CTGF), and IL8 can improve the uterine thickness (Oh, Kim et al. 2015).
Endometrial Scratching	human	Endometrial scratching before in vitro fertilization does not result in higher live birth rates in women undergoing a first embryo transfer (Pluddemann and Onakpoya 2020).
	human	Endometrial biopsy in the luteal phase was associated with an increased pregnancy rate after IVF (Gibreel, Badawy et al. 2013).
	human	Secretion of growth factors and cytokines involved in the wound healing process and may also contribute to embryo implantation. The increased chance of implantation is due to the enhancement of decidualization induced by endometrial scratching (Günther, von Otte et al. 2020).
	human	If performed in the pre-embryo transfer cycle, can balance the maturation and overgrowth of the endometrium caused by COH regimes during ART (Narvekar, Gupta et al. 2010).
	human	Accumulation of macrophages and neutrophils is associated with VEGF and Interferon secretion, and VEGF increases the vascularization of the decidua (Wheeler, Jena et al. 2018).
	human	Endometrial scratching in the luteal phase is associated with the highest rate of pregnancy in the next cycle. This effect may persist for a long time due to the presence of monocytes at the wound site (Vitagliano, Andrisani et al. 2019).
	human	Endometrial scratching on the day of ovulation can reduce successful IVF chances (Karimzade, Oskouian et al. 2010).
	human	Endometrial scratching did not significantly differentiate the clinical pregnancy rate (CPR) and live birth rate (LBR) in women who enter the ART cycle (van Hoogenhuijze, Kasius et al. 2019).
	human	Also has destructive effects on the receptive endometrium and embryo implantation on the day of ovulation. However, ES may increase CPR and LBR in women with the failure of two or more Fresh IVF ETs (Karimzade, Oskouian et al. 2010).
	human	Associated with acceptable results in women with unexplained infertility undergoing IUI (Gupta, Radhakrishnan et al. 2018).
	human	Retrieval day endometrial scratching improve clinical pregnancy and implantation rates (Ahmed Badawy 2020).
	human	Hsa-miR-449a, hsa-miR-3135b and hsa-miR-345-3p underly mechanisms by which acupuncture therapy help increase ER and promote endometrium receptivity (Mu, Li et al. 2020).
	human	Acupuncture before and after ET increased the pregnancy rates and Reduced anxiety levels (Guven, Cayir et al. 2020).
	human	Increase the blood flow to the ovaries and uterus and ultimately the endometrium (which is one of the characteristics of endometrial receptivity) (Guo, Wang et al.

acupuncture		2011).
	human	Enhances the endometrial receptivity by improving the endometrial morphology, and augmenting the uterine microcirculation, progesterone receptor regulation, and α7β3 integrin regulation, LIF, VEGF and HOX A10 (Zhong, Zeng et al. 2019).
	human	Increases the pregnancy rate by increasing the volume of the uterine blood flow (Zhang, Gao et al. 2014).
	human	Acupuncture was used as adjunctive therapy in addition to medical treatment, endometrial thickness was significantly increased. However, in most studies, if this intervention was used alone, it did not significantly change the endometrial thickness (Gu, Zhang et al. 2019).
	human	Acupuncture in women with a low and poor ovarian reserve and those who present with RIF had the best result. Indeed, acupuncture is used as a complementary treatment in the IVF cycle (Shuai, Li et al. 2019).
	human	Acupuncture has been used during ET and some during COH to increase the ovarian response to COH protocols increase the uterine receptivity, and increase the embryo quality (Wei, Liu et al. 2020).
Regenerative medicine	human	Use of eMSC obtained from the endometrial tissue or menstrual blood alone or in combination with PRP in RIF's patients can increase the endometrial thickness (kochar kaur, Allahbadia et al. 2020).
	rat	Increased its thickness, and expression of cytokines, vimentin, integrin, and LIF, which are markers of endometrial receptivity (Zhao, Zhang et al. 2015).
	human	sitagliptin, can be used to increase the abundance of eMSC during the implantation window (Tewary, Lucas et al. 2020).
	rat	Transplantation of UCMSCs promoted the repair of severe endometrial damage (Mei, Wuwen et al. 2020).