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Biochemical Indicators of Endometrial Receptivity in Uterine Function

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Abstract

Background: Endometrial receptivity is a critical prerequisite for successful embryo implantation and pregnancy, involving complex molecular interactions within the uterus. **Specific Background:** Implantation failure remains a major cause of infertility and recurrent implantation failure, despite advances in assisted reproductive technologies. Numerous biomolecules, including genes, proteins, microRNAs, extracellular vesicles, hormones, immune mediators, and microbial-related factors, have been investigated as indicators of uterine receptivity. **Knowledge Gap:** Although many biomarkers have been reported, comprehensive synthesis of recent evidence regarding biochemical indicators associated with receptive and non-receptive endometrium remains limited. **Aims:** This review aimed to summarizecontemporaryevidence regarding biomolecules associated with endometrialreceptivity and implantation success. **Results:** Analysis of studies published between 2019 and 2023 identified multiple biomarkers linked to receptive endometrium, including HOXA10, LIF, CTNNA2, annexins, integrins, mucins, osteopontin, CD44, IGFBP-7, CK7, extracellular vesicle-associated microRNAs, CD63, and progesterone-related pathways. In contrast, implantation failure was associated with reduced HSD17B2, AZGP1, TPPP3, S100A13, estrogen receptor β, progesterone receptors, and progesterone levels, alongside dysregulated immune profiles, altered microRNA expression, elevated CD9, oxidative stress, microbial disturbances, mitochondrial dysfunction, and cellular senescence. **Novelty:** This review integrates recent findings on genetic, proteomic, transcriptomic, immunological, hormonal, and extracellular vesicle-derived biomarkers relevant to endometrial receptivity. **Implications:** Identification and characterization of these biomarkers maysupportminimallyinvasive assessment of uterine receptivity, improve implantation prediction, and facilitate personalized management strategies for infertility and recurrent implantation failure.

Keywords: Endometrial Receptivity, Embryo Implantation, Recurrent Implantation Failure, Extracellular Vesicles, Biomarkers

Key Findings Highlights

Multiple genes, proteins, and extracellular vesicle contents were associated with successful implantation.

Recurrent implantation failure was characterized by molecular, immune, hormonal, and metabolic dysregulation.

Minimally invasive uterine fluid analysis provides promising approaches for receptivity assessment.

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Introduction

The normal endometrium becomes receptive to the embryo during the period of the window of implantation (WOI), which usually occurs seven days after the peak of LH and lasts for 2 to 6 days. The steroid hormones control the initiation of the period of WOI within the endometrium (1). After menstruation, the endometrium is in the proliferative phase, then becomes early secretory, mild secretory, and late secretory phases before the second menstruation (1).

Implantation failure may be due to the quality of the embryo, the endometrium, and their interactions. which may include chromosomal aberrations, maternal immune dysfunction, endometrial vascularization, and blood flow. The vascularization flow index is significantly higher in fertile women than in infertile women (2).

Embryo implantation in the endometrium requires three steps: apposition, adhesion, and invasion. During apposition, chemokines and other molecules in uterine fluid are important for crosstalk between the embryo and the endometrium. The adhesion step requires adhesion molecules such as integrins, mucin, and osteopontin. Steroid hormones, cytokines, and cell molecules regulate the invasion step (3). Therefore, different molecules can be considered as important biochemicals to accomplish uterine receptivity; failure of implantation means failure to achieve pregnancy and hence infertility, and the advanced methods to treat infertility, such as intrauterine insemination(IUI), in vitro fertilization(IVF), and intra-cytoplasmic sperm injection(ICSI), may end in implantation failure. Recurrent implantation failure means the failure to achieve pregnancy due to implantation failure for three times of transferring embryos in IVF procedures (4). The selected articles published between 2019 and 2023 are original research, clinical research, scientific reports, or meta-analyses involving human beings. Review articles and animal research are neglected. Forty-eight articles fit these criteria. This search is to show modern insights into molecules that may affect uterine receptivity.

Specimen collection and methods of determination

The following specimens can be utilized to determine endometrial receptivity:

1. Endometrial biopsy,
2. Uterine fluid,
3. Extracellular vesicles, and
4. Endometrial cervix.

1. *Endometrial biopsy:* this specimen is used for sequencing and analyzing DNA, RNA, or proteome analysis. The proteome analysis for endometrial tissue biopsy is done by two-dimensional differential in gel electrophoresis (DIGE), nanobore liquid chromatography-tandem mass spectrometry(LC-MS/MS), and isobaric tag for relative and absolute quantitation (iTRAQ). The iTRAQ LC-MS/MS technique detected 263 differentially expressed proteins related to implantation failure (5). The important genes are sequenced by the ERA test (6), the ER Map (7), the WIN-test (8), the be READY(1), and the TAC-seq. The pregnancy rate increased by 20% when blastocysts were transferred to the endometrium within the WOI time (9). The rs ERT, comprising 175 biomarker genes, showed an average accuracy of 98.4% (9).

2. *Uterine fluid:* contains extracellular vesicles, RNA, DNA, regulating proteins, ions, lipids, and other biofactors. 800 genes within the uterine fluid may be involved in implantation biology. The non-invasive RNA-sequence-based tests analyze transcriptomic profiles (10). The uterine fluid collection is a less invasive routine practice than tissue biopsy (11).

3. *Extracellular vesicles:* These vesicles are secreted from endometrial cells lining the glands and contain cargo, for example, lipids, proteins, and nucleic acids. These extracellular vesicles, known as exosomes (30-150 nm) or microvesicles (100-350 nm), are important for cell-to-cell communication (12). The isolation of endometrial secretome by uterine lavage, then isolation of extracellular vesicles by ultracentrifugation or sucrose cushion (13). This is a simple, non-invasive method and can be carried out during transvaginal ultrasonography during WOI (14)

The uterine fluid extracellular vesicles include genes known to regulate cell adhesion and implantation (10).

4. *Cervix biopsy:* The Human cervical epithelium during the period of pre-implantation exhibited an elevated level of LIF, which may be considered as a biomarker that detects uterine receptivity without invasive endometrial damage (15).

Biomolecules that are related to uterine receptivity:

Genes: The transcribed genes in fertile women differ from women with recurrent implantation failure. 122 differentially expressed genes are downregulated, and 66 are upregulated in women with recurrent implantation failure(16). Moreover, the genes that interact with many other genes and are most closely associated with the disease, called hub genes, may play an important role in recurrent implantation failure. The genes strongly correlated with signaling pathways and immune response in recurrent implantation failure are three to ten hub genes(16,17). The immune pathways were significantly downregulated, while lipid metabolism pathways were significantly upregulated in those patients(17). 72 genes determine endometrial receptivity, four of which are housekeeping genes (genes that are expressed in all cells in normal and pathological conditions for cellular basic function). can be sequenced using using uterine fluid-derived extracellular vesicles transcriptome (18) or by using uterine biopsy (1). The examples of important genes are as follows:

1. The HOXA10 gene, one of 39 genes of the homeobox (HOX) gene family responsible for embryonic development, is crucial for embryo implantation and decidualization and encodes the Homeobox protein Hox-A10, which is important for protein binding and DNA binding (19).
2. The LIF gene(leukemia inhibitory factors) encodes for the pleiotropic cytokines important for hematopoietic differentiation, leukemia cells' terminal differentiation, induction of neural cell differentiation, and the immune tolerance at the maternal-fetal interface (15).
3. CTNNA2 (catenin alpha 2) gene is important for uterine receptivity (20). The CTNNA2 is a protein-coding gene that regulates cell-cell adhesion between cadherin adhesion receptors and the cell cytoskeleton (21).
4. The ZEB1 gene encodes a zinc finger transcription factor that binds the HOXA10 gene, controlling its expression and modulating endometrial receptivity through epithelial-mesenchymal transition promotion. The ZEB1 gene is highly expressed at mRNA and protein levels in human endometrium during the mid-secretory phase of the menstrual cycle. Also, it promotes mesenchymal transition in carcinogenesis (22).
5. Moreover, higher expressions of ABCG2 and ALDH1A1 genes are detected in the receptive women's uterus. The ABCG2 gene encodes proteins for heme transport and protein binding. The ALDH1A1 gene encodes proteins for the metabolic retinol process and oxidoreductase activity (23).
6. The transition from the pre-receptive to the receptive phase of the endometrium showed an altered expression of certain genes such as ICAM1, NFKB1A, UCAM1, LIF, VEGF, and TLR5+, suggesting their enrollment in the endometrial receptivity (24).

2. Proteins

The uterine fluid proteins can be used to estimate uterine receptivity. A study revealed that over 3000 proteins can be found in uterine fluid. 367 of these proteins undergo significant alterations when the endometrium is transformed from early secretory endometrium to mid-secretory endometrium (the window of implantation). While women with recurrent implantation failure showed an altered mid-secretory endometrial profile in the uterine fluid after proteomic analysis using mass spectrophotometry (25)

The extracellular vesicles are important for uterine receptivity. These vesicles can be isolated by ultracentrifugation. 218 proteins were present in the extracellular vesicles, and 82 were selected as novel biomarkers for endometrial receptivity (26). These proteins may include annexins, collagen VI, integrins, mucins, and profilin 1. Annexins are upregulated during the receptive endometrial phase and act as adherent molecules between the embryo and endometrium, while integrins mediate cell adhesion to collagens and laminin. The profilin 1 expressed by endometrial epithelial cells is necessary for embryo attachment, while other metalloproteinase proteins affect tight junctions in trophoblastic cells. Moreover, integrin αvβ3, vascular endothelial growth factor (VEGF), tumor necrosis factor-alpha (TNF-α), and leukemia inhibitory factor (LIF) in uterine fluid were higher in fertile women. Integrin αvβ3 has the best prediction value for endometrial receptivity among other biomarkers (2)

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Integrins are molecules important in cell-cell adhesion and cell-extracellular matrix adhesion. At the beginning of pregnancy, integrin expression is important for trophoblast attachment and embryo invasion of the decidua (27). Several integrin types act alongside other cell adhesion molecules such as selectins and cadherins. The integrin is a U-shaped structure embedded in the cell membrane, hooking other molecules and signaling cells for attachment, differentiation, or death (28).

Mucin 1 and cyclooxygenase-2 in the endometrial tissues are the most direct functional molecules and the final effector of transcriptional gene translation (5). Mucin 1 glycoprotein is required for adhesion, while mucin 16 overexpression on the endometrial cell surface may hinder implantation (29). The enzyme, cyclo-oxygenase-2, converts arachidonic acid to prostaglandin E2, an important molecule for implantation, and decidualization (30).

Other proteins, such as osteopontin and CD44, play a significant role in uterine receptivity. The CD44 is a transmembrane glycoprotein important for the migration and adhesion of endothelial cells. Osteopontin is a phosphoglycoprotein that acts as a bridge between the endometrium surface and trophoblast through interaction between αvβ3 integrin and CD44. CD44 and osteopontin are increased in the secretory phase in the endometrial tissue of fertile women during the window of implantation to form a complex that is important in embryo recognition (31)

Moreover, the legumina protein, the cysteine endopeptidase that hydrolyzes asparaginyl bonds, may regulate trophoblast invasion and endometrial remodeling. The glycoprotein IGFBP-7 may regulate the IGF-1 metabolism, interact with IL-6 expressed in the endometrium, and play an important role in decidualization. Hepatocyte growth factor is important for cell proliferation because it binds to hepatocyte growth factor receptors. CK7 (cytokeratin 7) is upregulated threefold in the receptive endometrium (32).

A protein that MLL1(mixed lineage leukemia 1 protein), a DNA transcription factor that regulates transcription of HOX genes, functions as a methyltransferase. The EZH2 protein, a histone-lysine N-methyltransferase enzyme encoded by the EZH2 gene, acts as a negative regulator of DNA-binding transcription factors (33). The ratio of MLL1:EZH2 was low in the uterine secretions of non-receptive women. because EZH2 inhibits HOXA10 expression and decreases decidualization, but MLL1 has an important role in the downstream effect on the HOXA10 gene (19).

There are 263 differentially expressed proteins in the endometrial tissue of patients with recurrent implantation failure (5). The 17b-hydroxysteroid dehydrogenase (HSD17B2), zinc-α-2-glycoprotien (AZGP1), tubulin polymerization-promoting protein family member 3 (TPPP3), and S100A13 are significantly lower in the non-receptive uterus; therefore, they may be considered as key biochemical markers for endometrial receptivity and diagnosis of recurrent implantation failure (5,34). HSD17B2 is an enzyme responsible for the synthesis and inactivation of estrogen and androgen, the production of active progesterone, and the oxidation of estradiol to estrone. This enzyme is located in the endoplasmic reticulum and is expressed in glandular and luminal cells. The AZGP1 protein is a secretory adipokine regulated by the thyroid, androgen, and glucocorticoid hormones. It is important for lipolysis, glucose transport, and low inflammatory factors. The TPPP3 is located in the nucleus and expressed in endometrial ciliated cells, stabilizing the integrity of the microtubule system, the main component of the mitotic spindle that controls cell division and aggregation. And, S100A13 is a small calcium-binding protein important for calcium homeostasis and cell proliferation (5,34). 82 differentially expressed proteins in women with recurrent implantation failure, 55 proteins upregulated, and 27 downregulated (35). The presence of Cystatin B, the intracellular inhibitor of thiol proteinase cathepsin B, is associated with miscarriage (32). The CBG(cortisol binding globulin) and the Fetuin-A protein show higher levels in recurrent implantation failure (35). CBG is important for cortisol delivery, inflammation, and metabolism; its increase may be related to low progesterone levels. Fetuin-A is the major carrier of free fatty acids, important for free fatty acid-induced insulin resistance (36) and decreases embryo implantation (35). Another protein that decreases uterine receptivity is podocalyxine, expressed by the human endometrial epithelium. This protein decreases implantation by rendering the epithelium nonadhesive. Moreover, this protein may suppress gene expression of cell adhesion (LIF), stimulate anti-implantation genes such as LEFTY2, and increase expression of adherence and tight junction proteins such as E. cadherin and claudin. Finally, the luminal epithelium must switch to the receptive phase during the window of implantation (37).

miRNA: The mature miRNAs or microRNAs are small noncoding regulatory RNAs (19-25 nucleotides) that regulate hundreds of mRNA molecules by inhibition or translation promotion, or by degradation of mRNA. The miRNA can be quantified by real-time PCR (38). These molecules participate in angiogenesis by modulating the expression of proteins that promote vessel growth(39). The dysregulated miRNAs result in implantation failure (40), as they are present in extracellular vesicles in uterine fluid, which modulate implantation by affecting target genes in epithelial cells (40). Therefore, miRNAs act as epigenetic regulators of endometrial receptivity and embryo implantation through post-translational modification .

A study on the endometrial fluid used the endometrial receptivity array technique that depends on tissue gene expression of microRNA by using real-time PCR during the window of implantation, found that 61 miRNAs are dysregulated in women with recurrent implantation failure when compared to healthy women, 34 are upregulated, and 27 are downregulated (40). After ultracentrifugation and separation of extracellular vesicles from uterine fluid, 12 endometrial extravascular small noncoding RNAs were identified. These modulate endometrial receptivity and control the immune response, extracellular matrix remodeling, and cell junction(12). On the other hand, a small noncoding RNA (hsa-miR-362-3p) is highly expressed in non-pregnant women with implantation failure. while the miR-183 family showed estrogen-dependent upregulation in endometrial cells, with a positive effect on cell migration and proliferation. The miR-183-5P regulates the endometrial cells' CTNNA2 gene and enhances estrogen's effect on endometrial receptivity (20). The natural cycle and hormone replacement therapy cycle showed the same miRNA expression (41).

Immune cells: A study revealed that 75% of recurrent pregnancy loss is usually due to a dysregulated immunological profile that, when treated, increases live birth to 55% in those women (42). Innate immune cells such as natural killer cells, macrophages, and dendritic cells are abundant at the implantation site. These cells express toll-like receptors (TLRs) that, when stimulated, result in the expression of anti-inflammatory cytokines. The expression of TLR signaling molecules differed between fertile women and those with recurrent implantation failure (24). while the infiltration of CD56 natural killer cells, dendritic, Th1, Th2, regulatory T cells, and macrophages in the endometrium in recurrent implantation failure decreased (17).

The uterine natural killer cells (uNK) aid in trophoblast invasion (43). That CD56+ uNK cells correlate with the transcriptional markers of endometrial receptivity assessed by gene expression (44). while CD16+ natural killer cells resulted in embryo rejection in infertile women (16), and a very high level of uterine natural killer cells is a predictor of miscarriage (43).

The T-helper cells' cytokines (Th2 cytokines) favor the implantation process, while the T-helper cytokines(Th1 cytokines) are harmful for implantation(43). The CD20 receptors of B-cells are increased in abortion, as the B-cell activation plays an important role in repeated implantation failure (32).

The immune profile of the endometrium is hyper-activated, hypo-activated, or a mixed immune profile. The hyper-activated profile resulted in pregnancy loss by direct rejection of the embryo. The mixed profile is characterized by immune over-activation, excess of Th1 cytokines, but immature uNK cells (42). The hyper-activated or hypo-activated immune profile depends on the maturation of uterine natural killer cells, and the increase of IL-15 is a marker of uNK cell activation (43).

Surface markers:

CD9 is a cell surface glycoprotein containing a palmitoylation site that allows cells to interact with lipids and proteins such as integrins and negatively regulate cell proliferation (45). CD63 is a protein associated with the membrane of intracellular vesicles or cell surface expression. It can be expressed in stromal cells of the endometrium and functions in protein binding and positive regulation of integrin-mediated signaling pathways (46). The exosomes (30-100 nm) in the uterus are secreted from the endometrial epithelium, contain miRNA, and exhibit cell surface markers CD63 and CD9. Exosome production in the mid-secretory phase increased to enhance implantation. CD63 increased in fertile women, peaking during the implantation window, while CD9 expression increased in non-receptive women and is considered a biomarker of infertility (47).

Receptors:

There are two types of estrogenic receptors in the endometrial tissues: ERα and ERβ. The ERα receptors are expressed during the follicular phase

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of the menstrual cycle. The ERβ receptors, the dominant estrogen receptor subtype expressed within the vascular endothelium during the window of implantation. These receptors are important for angiogenesis and vascular remodeling. The study of Hannan Al-Lamee et al. (48) found that infertile women have a lower level of estrogen receptor type (ERβ) and progesterone receptors. Conditions that lead to decreased estrogen levels, such as GnRH agonists, may result in a significant reduction of endometrial progesterone receptors and ERβ, which leads to infertility (48).

Steroid hormones:

The endometrial receptivity window is within the mid-secretory phase after sufficient time from progesterone exposure. The progesterone inhibits cholesterol synthesis and epithelial cell proliferation during the mid-secretory phase. Moreover, abnormal progesterone signaling leads to infertility and other gynecological diseases (49).

The binding of progesterone with the progesterone receptors resulted in the activation of the expression of PGR-regulated genes such as homeobox gene (HOXA10), bone morphogenesis protein 2(BMP2), MMP2, SERPINE1, MNMT, WNT5A, EMP1, and IER3. Moreover, numerous epithelial cell surface markers are upregulated and presented upon PGR binding, such as CLDN4, CLDN8, and KLF4 (49). Within 72 hours, progesterone release downregulates podocalyxin protein, an adhesion transmembrane sialomucine and negative regulator of uterine receptivity (50). During low progesterone levels in endometrial non-receptive phases, podocalyxin protein increased and rise epithelial polarity. This protein should be decreased during the window of implantation period when the endometrium becomes receptive (50). The administration of progesterone and human chorionic gonadotrophin (hCG) after ovarian stimulation resulted in increased VEGF level and miR-17-5P, which stimulate the angiogenic pathway, endometrial vascular activity, and endometrial receptivity (39).

Progesterone increases the expression of 17β-hydroxysteroid dehydrogenase enzyme (HSD17B2), while low progesterone levels cause overexpression of cortisol-binding globulin (CBG), which dysregulates endometrial immune conditions (34,35). However, the infertile women showed lower levels of HSD17B2 and higher estradiol levels than fertile women(34). Also, the level of the mid-luteal estradiol is inversely related to markers of endometrial receptivity maturation (44).

Cytokines, microbiota, and infections:

idiopathic infertility showed lower levels of TGFβ1 (transforming growth factor), bFGF2 (fibroblast growth factor basic), and a high level of DEFa1 (α-defensin). The expression of these markers is correlated with the presence of endometrial peptostreptococcus, human papilloma virus (HPV), history of recurrent human simplex virus infection (HSV), and miscarriage (51).

TGFβ1 (transforming growth factor) is an extracellular multifunctional polypeptide cytokine produced by white blood cells that controls cell growth, proliferation, differentiation, and T-cell regulation (52). The bFGF2(fibroblast growth factor basic) interacts with the transmembrane receptors such as integrin and influences cell proliferation and tissue vascularization. The FGF2 expression increases in the glandular epithelium of the secretory phase of the endometrium of fertile women, acting as an integrin ligand important for adhesion, development, differentiation, and angiogenesis (53). The DEFa1(α-defensin) is produced by neutrophils and epithelial cells upon infection. It is an inducible bacteriolytic protein that acts on gram-positive and gram-negative bacteria (54).

Furthermore, it is found that Enterococcus faecalis, especially with superoxide-producing E. faecalis, may result in opportunistic chronic endometritis and lead to infertility because of its effect on the expression of cytokines that promote apoptosis and damage uterine receptivity (55). Therefore, uterine cavity infection may alter cytokine pathways necessary for blastocyst development and implantation (51). Women with recurrent HSV, HPV, miscarriage, and chronic endometritis should undergo an assessment of their immune biomarkers (51,55).

Oxidative stress:

The total antioxidant status and enzyme prolidase enzyme activity were higher in patients with unexplained infertility. Parolidase enzyme is important for protein metabolism, matrix remodeling, inflammation, angiogenesis, and cell proliferation. The enzyme parolidase is increased in oxidative stress and can be used as an oxidative stress marker in various diseases (56)

Other factors:

Implantation failure is highly associated with the down-regulation of the ribosomal proteins, mitochondrial dysfunction, and abnormal metabolic processes of hormones and lipids (5). The normal metabolism and mitochondrial function are important for successful embryo implantation. Therefore, lysophosphatidic acid receptor 3 and glucose transporter 1 were linked to endometrial receptivity (5). In general, women with recurrent implantation failure had lower vitamin D levels, border lower progesterone levels, and more vaginal microorganisms compared with controls (57)

Effect of age and gynecological disease on the endometrial receptivity

Aging:

The endometrial aging is completely different from individual age; the implantation failure may be induced by stress, oxidative stress, or DNA damage (23). Sixteen human genes are expressed with the aging of the endometrium (58). The non-receptive endometrial cells consist mainly of senescent cells(cells that stop multiplying, do not die, but release chemicals that trigger inflammation, increase the expression of mRNA of CDKN1A genes, and expression of senescence secretions). The CDKN1A gene is important in DNA damage, cell death, cellular senescence, cytokine-mediated pathway, and negative regulation of vascular proliferation(59).

On the other hand, autophagy is essential for embryo implantation (60). Autophagy is the breakdown of old cells in the body and their reuse so that cells operate more effectively. This is highly present in normal human proliferative, secretory, and decidual tissue, manifested by autophagy-related markers.

Polycystic Ovary Syndrome(PCOS) and Uterine Receptivity:

Women with PCOS may have infertility due to abnormal expression of certain receptors, such as alpha-v-betal-3 receptors(α v B3), a type of integrin that acts as a receptor for phagocytosis on macrophages and dendritic cells, and lysophosphatidic acid receptor 3 (LPAR3). which is a protein-coupled receptor that binds the lipid signaling molecule lysophosphatidic acid and evokes calcium mobilization. The abnormality of these receptors in PCOS may be reversed by berberine or metformin (61). The lipid metabolism-related genes can modulate embryo implantation by affecting adhesion molecules, adipokines, and other lipids. The abnormality of lipid metabolism in women with PCOS, and hence the implantation failure, can be treated by lovastatin administration or quercetin due to their effect on blood lipids (62). Moreover, the lifestyle modification in PCOS may modulate endometrial proteomes, such as an increase of legumain, insulin-like growth factor receptors, keratin, type II cytoskeletal 7, and cystatin B, and a decrease of CD20 beta lymphocyte antigen (32). Also, downregulated genes in the receptive endometrium showed more downregulation in obese PCOS upon weight loss (63).

In polycystic ovarian syndrome, the levels of osteopontin and CD44 receptors are increased in circulation and local secretions, which leads to implantation failure, because of saturating osteopontin and CD44 receptors on the surface of blastocysts (31). However, a study showed that women with recurrent implantation failure, whether PCOS or not, undergo a displacement or transition in the window of implantation time (1).

Endometriosis and Uterine Receptivity:

The impaired endometrial receptivity in women with endometriosis may be related to gene polymorphism of muc-1 and COX-2 (64). Women with endometriosis showed upregulation of six proteins associated with endometrial receptivity. Metformin treatment upregulates insulin-like growth factor binding 7(IGFBP-7). Therefore, metformin may enhance endometrial receptivity in endometriosis by improving the expression of endometrial receptivity marker IGFBP-7(64).

Anti-phospholipid syndrome:

Women with anti-phospholipid positivity exhibit recurrent implantation failure due to their inhibition of LIF and HOXA10 expression, or due to abnormal uterine pinpode development during the window of the implantation period(65).

Treatment of recurrent implantation failure

Immune hyperactivated women are treated with prednisolone 20 mg/day, vitamin E twice a day, and high doses of progesterone to decrease the expression of pro-inflammatory cytokines. The treatment with prednisolone continues until 8 weeks of pregnancy because it decreases Th1 cytokines and IL-15 mRNA overexpression. Heparin can be effective by modulating the complement effect. The intravenous Intralipid can be used

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with high-dose progesterone to decrease immune activation and increase the Th2 effect (42).
The treatment of hypo-activated women is done by endometrial scratching and administration of HCG injection 1500 IU on days 4,6, and 8 after oocyte retrieval for women undergoing IVF to trigger the maturation of uNK cells (61), also sexual intercourse is recommended (42,43).
The procedure of platelet-rich plasma treatment may increase uterine receptivity because of the increased expression of microRNA (miR-211-3p), which increases the chances of pregnancy. However, the increase in IGF-1 levels after platelet-rich plasma treatment is related to poor pregnancy outcomes (38).
Metformin is recommended to increase uterine receptivity for women with minimal to mild endometriosis(66) and women with PCOS (61). Also, the low uterine receptivity of PCOS women can be treated by berberine, Lovastatin, and quercetin (61,62).

Conclusion

No single molecule or receptor can affect uterine receptivity, but huge numbers of mediators can. Certain gynecological diseases may affect uterine receptivity, such as endometriosis and PCOS, or it may be due to unknown causes. Aging of women is not related to endometrial receptivity but rather endometrial aging. Different biomolecules may affect uterine receptivity, such as certain genes, their transcriptional molecules, proteins, receptors, hormones, uterine fluid microvesicle contents, and miRNAs. Moreover, infection, immunity, and microbiota play important roles in this respect. Characterization and identification of biomarkers important for the receptive endometrium increase the probability of successful embryo implantation.

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