Chapter

The Genetic and Biochemical Blueprint of Endometrial Receptivity: Past, Present, and Future Factors Involved in Embryo Implantation Success

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Abstract

In the field of assisted reproductive technology, endometrial receptivity is a crucial aspect that affects implantation rates in *in-vitro* fertilization procedures; in fact, impaired endometrial receptivity has been identified as the rate-limiting step for favorable pregnancy outcomes once factors regarding embryo quality have been optimized. The endometrium is a dynamic tissue that undergoes proliferative and secretory changes in each menstrual cycle, acquiring a short and transient period of embryo receptivity known as the Window of Implantation. Precise embryo-endometrial synchrony is necessary to achieve a successful pregnancy, and it involves complex and multifactorial processes related to morphological, biochemical, and genetic changes. On that behalf, defining the receptive window of each patient for personalized embryo transfer is a current goal. Here, we review different indicators of endometrial receptivity throughout the menstrual cycle, spotlighting the opening of the window of implantation: classical histological and biochemical markers, genetic factors, leading-edge transcriptomic signatures and miRNA profiles, and novel features such as the microbiome and secretome. Understanding the molecular mechanisms behind endometrial receptivity will facilitate the optimization and improvement of infertility treatments.

Keywords: endometrial receptivity, embryo implantation, menstrual cycle, window of implantation, decidualization

1. Introduction

The field of assisted reproductive technology (ART) has grown significantly in use and understanding over the past few decades, nevertheless, the rates of successful pregnancies in *in-vitro* fertilization (IVF) procedures are still relatively low. Impaired endometrial receptivity (ER) has been identified as the rate-limiting step for favorable pregnancy outcomes once all other factors, including the acquisition and selection of the best quality embryo(s), have been optimized. Correct and synchronized maturation of the endometrial tissue is essential for embryo

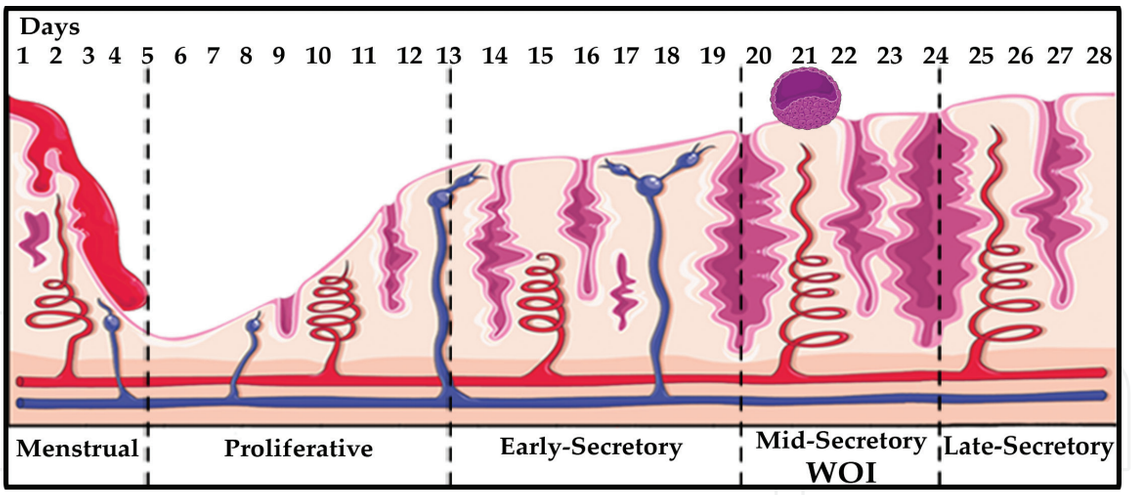

Figure 1.
Endometrial dynamics throughout the menstrual cycle. This picture was modified from Servier Medical Art under the Creative Commons License 2018.

implantation [1, 2]. The endometrium is a dynamic tissue that undergoes proliferative and secretory changes in each menstrual cycle. Throughout most of this cycle, the endometrium remains "non-adhesive" to embryos and it only acquires a short and transient period of embryo receptivity known as the "window of implantation" (WOI) [3, 4]. In humans, during a natural cycle, the endometrium becomes receptive 6 to 8 days after ovulation and it remains receptive for approximately 24–48 h, this time is assumed to occur between days 20 and 24 of a regular menstrual cycle [2, 5] (**Figure 1**). The cyclic fluctuations of the endometrium are coordinated by the ovarian hormones estrogen (E2) and progesterone (P4); a finely balanced signaling process mediated by these hormones defines the WOI. The menstrual cycle is divided in two phases: proliferative or follicular, and secretory or luteal [6]. During the proliferative phase (PP), E2 from the maturing follicle allows the elongation of the spiral arteries and the proliferation of endometrial stromal cells (EnSCs) and glands [7]. Afterwards, during the secretory phase (SP), P4 from the corpus luteum induces secretory changes; the endometrium thickens and it acquires a receptive phenotype that will support blastocyst attachment [8–10]. During the Mid-Secretory Phase (MSP) circulating P4 induces EnSCs to undergo decidualization [11]. Decidualization is the transformation of the endometrial stroma into a dense cellular matrix known as the decidua, this process initiates during the SP in the stroma and, if pregnancy occurs, it progresses into the development of the decidua which will in turn form the maternal placenta [12]. The optimization of the endometrium to support embryo implantation is a complex and multifactorial process that involves morphological, biochemical, and genetic changes [13]. ER is a key aspect that affects implantation rates in IVF procedures considering that a precise embryo-endometrial synchrony is completely necessary to achieve a successful pregnancy [4, 14]. Thus, understanding the molecular mechanisms behind ER will facilitate the optimization and improvement of infertility treatments.

2. Factors involved in endometrial receptivity

2.1 Evaluation of endometrial morphology for receptivity assessment

Morphological changes during the endometrial cycle generate markers that have been used over decades to assess receptivity, such as histological evaluation of a biopsy and ultrasound examination of the endometrium. Endometrial biopsies are now

considered to provide little clinically relevant information [15, 16]. Additionally, the formation of pinopodes was thought to show potential as a clinical marker to assess ER [17]. However, the presence of pinopodes was demonstrated not only during the WOI but also in the post-receptive endometrium, precluding in this way its use as a marker of ER [17, 18]. On the other hand, ultrasound examination is a routinely used technique in IVF procedures [9, 19]. This non-invasive technique is based on the interpretation of a medical ultrasound of the endometrium. Various ultrasonographic parameters have been proposed as pregnancy predictors, such as endometrial thickness, volume, and blood flow patterns. The most commonly used is endometrial thickness [20, 21]. Due to differences in stimulation protocols, sonographic approaches, and difficulties in obtaining a standard sagittal view of the uterus, discrepancies in the cut-off value of endometrial thickness to achieve pregnancy arise [22]. Generally, it is considered that a minimum of 6–8 mm in endometrial thickness is necessary for a successful pregnancy [23–25]. Nevertheless, case reports have described pregnancy establishment despite an endometrial thickness of no more than 4 mm [26, 27]. Three-dimensional (3D) sonography assesses ER by considering endometrial thickness, volume, and angiogenic dynamics. The endometrial volume of fewer than 2 ml has been shown to decrease pregnancy rates significantly [19, 28, 29]. Another evaluated criterion is an endometrial pattern, which can be classified as triple-line, intermediate, or homogenous [30]. Among these, the triple-line pattern has been suggested to reflect ER [24, 31] broadly. Finally, the impact of ovarian stimulation on ER has yet to be determined. Abnormal hormone concentrations the due to stimulation protocols during IVF might affect endometrial morphology and thereby ER [32]. Comprehensively, although morphological elements are important components of receptivity, there is still no consensus on the extent in which they can be used as WOI predictors.

2.2 Genetic factors involved in ER

Endometrial genetic abnormalities can lead to implantation failure due to dysregulation of critical processes such as trophoblast invasion and angiogenesis. Here, we discuss common genetic abnormalities that have been analyzed to determine their role in implantation failure (**Table 1**). Parental chromosomal abnormalities such as mutations and translocations should be considered relevant in the efficacy of improving reproductive outcome.

2.2.1 Angiogenetic factors: vascular endothelial growth factor (VEGF), endothelial nitric oxide synthase (eNOS), TP53 tumor suppressor (TP53), murine double minute 2 (MDM2), herpes virus-associated ubiquitin-specific protease (HAUSP)

Successful pregnancy is dependent on adequate placental circulation and fetal vasculature. The development of a normal vascular network during implantation, embryo development, and placentation requires cooperation between different cell types and various growth factors. *VEGF* is a potent angiogenic factor that plays an essential role in embryo implantation/development. Four *VEGF* polymorphisms have been reported to affect VEGF activity and expression increasing aberrations in vascular formation and/or function. The polymorphism −1154G/A located in the promoter region has been associated with RPL [33], RSA [34, 35], and RIF [36, 37]. Moreover, a meta-analysis showed that genotypes −2578C/A, −634G/C, and 936C/T increase the risk of RSA as well [38]. Furthermore, *eNOS,* which is expressed in the terminal chorionic villous vessels, is important for vascular nitric oxide (NO) production to supply nutrients to the fetus. Only the eNOS Glu298Asp polymorphism has been shown to be significantly associated with RPL [39]. Additionally, successful trophoblast invasion requires the induction of paracrine apoptotic reactions to

Gene	Polymorphism	rs code	Relevance	References
APOE			Heterozygous genotype is more frequent in women with RPL	[33]
eNOS	VNTR (B/A)		Association to the risk of RPL	[77]
			No associated	[78]
	Glu298Asp		Homozygote genotype T/T is associated with risk of IRM	[39]
ESR1	IVS1-397T>C	rs2234693	Related to unknown thin endometrium in which P allele may be the risk and X allele its guard factor	[44]
	IVS1-351A>G	rs9340799		
F2	G20210A	rs1799963	No association	[58, 60, 62, 63]
			Heterozygous genotype is more frequent in women with RSA in the first trimester [57] and women with RPL [42]	[42, 57]
F5	G1691A, Leiden	rs6025	No association	[57, 58, 62, 63]
			More frequent in women with RIF	[60]
	H1299R (R2)		No association	[58, 62, 63]
	Y1702C		No association	[58, 62, 63]
F8	V34L		More prevalent in women with RPL	[42, 58]
			No association	[62, 63]
FGB	G-455A	rs1800790	No association	[57, 58, 62, 63]
GPIIIa	C1565T		No association	[57]
HAUSP	rs1529916 G/A	rs1529916	Allele A is associated with RIF	[40]
HPA1	HPA1 a/b (L33P)		No association	[58, 62, 63]
LIF	C715A		No associated	[72]
	G3400A		More frequent in nulligravid women	[72, 73]
	G3424A		No associated	[72]
	T1414G	rs929271	G/G genotype is associated with RIF	[40, 74]
MDM2	T309G	rs2279744	Allele G is associated with RIF	[40]
MTHFR	A1298C	rs1801131	No association	[58, 62–64]
	C677T	rs1801133	More frequent in women with unexplained infertility [64], RPL [42, 58], and RSA [60]	[42, 58–60]
			No association	[57, 62, 63]
MUC1	VNTR		Women with unexplained infertility might have susceptibility to implantation failure due to small *MUC1* allele size	[67]
			No association	[68, 69]
MUC4	VNTR		No association	[70]
PAI-1	4G/5G	rs1799889	More prevalent in women with RIF [63] and RPL [42, 58]	[42, 58, 63]
			No association	[62]

Gene	Polymorphism	rs code	Relevance	References
PR	H770H-C/T		No association	[54]
	G/T—Val660Leu	rs1042838	More prevalent in women with unexplained infertility	[65]
	V660L		No association	[54]
PT53	Codon 72 Pro	rs1042522	Homozygote genotype is associated with RPL [41, 75], IRM [76] and RIF [37, 40]	[37, 40, 41, 75, 76]
	Codon 72 Arg	rs1042522	Homozygote genotype is associated with RIF	[75]
PTGS2	G-765C	rs20417	Association with implantation failure susceptibility	[55]
TFF3	rs225361 A/G	rs11701143	Homozygous genotype is associated with less live births before their first spontaneous abortion	[61]
	rs225361 A/G	rs11701143	No association	[66]
	rs11701143 T/C	rs225361	Associated with idiopathic RSA	[61]
	rs11701143 T/C	rs225361	No association	[66]
	rs225439 G/A	rs225439	No association	[61, 66]
	ros533093 C/T	rs533093	No association	[61, 66]
	rs77436142 G/C	rs7743614	No association	[61, 66]
VEGF	G-1154A	rs1570360	Homozygote A/A genotype associated with RSA [34, 35], RPL [33], and RIF [36, 37]	[33–37]
			No associated	[71]
	C-2578A	rs699947	No associated	[34]
	G-634C	rs2010963	No associated	[34]
	C936T	rs3025039	No associated	[34]

Probably implicated mutations in implantation failure, studies are listed even when no association was found, rs code is mentioned whenever it is reported.

Table 1.
Genetic abnormalities involved in implantation failure.

secrete proteases capable of digesting the endometrial extracellular matrix (ECM) [36]. TP53 is a potent regulator of apoptosis, cell cycle, angiogenesis, and embryonic development. A TP53 polymorphism at codon 72, encoding either proline or arginine, was reported to alter the TP53 activity and affect human fertility [40]. The Arg72 variant has been shown to induce higher apoptotic activity than Pro72. Therefore, Pro72 variant might cause inadequate trophoblast invasion, increasing the risk of RPL [41] and RIF [37, 40]. In this manner, women with Pro/Pro genotype have a higher risk of RPL than women with the Arg/Arg or Arg/Pro genotypes. Following, MDM2 and HAUSP regulate TP53. MDM2 binds to TP53 to degrade it through poly-ubiquitination, blocking its ability to function as a transcription factor. The *MDM2* SNP309 is a functional SNP that increases MDM2 expression levels and attenuates TP53 pathway. HAUSP, on the other hand, acts as a specific deubiquitinase for TP53, the A allele has a significant association with infertility in young patients (<35 years) but not in the older patients, similarly to the *MDM2* SNP309 G allele. Those observations suggest that *MDM2* and *HAUSP* may be involved in the regulation of human fertility through the regulation of TP53 [40].

2.2.2 Apolipoprotein E (APOE)

Due to the increase in total cholesterol levels during pregnancy, *APOE* plays a crucial role in lipid metabolism. *APOE* has three alleles in the long arm of chromosome 19 at position 13.2: ε2, ε3, and ε4. Individuals harboring the allele ε4 have higher cholesterol levels than the ones carrying the ε3/ε3 allele, whereas levels in those with the ε2 allele are lower [42].

2.2.3 Estrogen receptor α (ESR1)

ESR1 is a ligand-activated transcription factor essential for sexual development and reproductive function; its dysregulation leads to the development of various diseases such as cancer, cardiovascular disease, and inflammation, among others [43]. Due to alternative splicing of mRNA, it possesses three isoforms: ERαΔ3, ERα36, and ERα46 [43]; in a study performed by Yuan and Le [44], the polymorphisms rs2234693 and rs9340799 were related to the uncommonly thin endometrium.

2.2.4 Leukemia inhibitor factor (LIF)

LIF is an important implantation factor that promotes proliferation, invasion, and differentiation; its expression is regulated by the transcription factor tumor protein TP53 (TP53). Few studies have found a correlation between LIF gene polymorphism and reproductive capacity, Kang et al. demonstrated that SNP in the 3'UTR of the LIF (rs929271) gene is associated with infertility [40].

2.2.5 Mucin 1 (MUC1), Mucin 4 (MUC4)

MUC1 is an anti-adhesion molecule secreted by human endometrial epithelium, it has been suggested that its expression prevents the adherence of blastocyst to the endometrium. Interestingly, MUC1 must be locally removed in a paracrine fashion at the implantation site during the WOI to allow contact between the embryo and the endometrium, making it an important factor in determining ER [45–48]. *MUC1* is a highly polymorphic gene that differs in the size of the region carrying the O-glycosylation sites: the variable number tandem repeat region (VNTR), which can go from 20 to 125 repeats [49]. Similarly, MUC4 is a greatly expressed mucin in endometrial epithelium [50], its gene is highly polymorphic and it contains a VNTR region that can go from 145 to 395 repeats [51]. Although its role in human infertility has not been fully explored, studies in other species have suggested that it plays a role in embryo implantation [52, 53].

2.2.6 Progesterone receptor (PR)

The PROGINS complex are three mutations in the *PR* gene that may be associated with unexplained infertility and implantation failure: a 306 bp insert in intron G of the dT2 allele in *PR*, the mutated alleleV660L, and guanine to thymine substitution in exon 4, resulting in a valine to leucine change in the hinge region of PR, and a cytosine to thymine substitution at exon 5 [54].

2.2.7 Prostaglandin-endoperoxide synthase 2 (PTGS2)

PTGS2 is a key enzyme involved in the conversion of arachidonic acid to prostaglandins (PGs). The −765G>C SNP mutation in the promoter region of *PTGS2* upstream the transcriptional start site in the putative Sp1 site can cause alterations in Sp1 binding

[55]. Accordingly, the hypermethylation of the NF-IL6 site within the *PTGS2* promoter results in elevated gene expression in eutopic endometrium in endometriosis [56].

2.2.8 Thrombolytic factors: coagulation factor II (F2), coagulation factor V (F5), coagulation factor XIII a chain (F13A1), methylenetetrahydrofolate reductase (MTHFR), plasminogen activator inhibitor-1 (PAI-1)

Thrombophilia, the predisposition for thrombosis, has been shown to be a risk factor for successful pregnancy due to impaired vascularization at the time of implantation. Therefore, the possible association between early pregnancy loss and polymorphisms at coagulation factors and thrombolytic genes responsible for inherited or acquired thrombophilia has been investigated. The coagulation factor II SNP G20210A in the 3′-untranslated region of *F2* causes elevated prothrombin in plasma, leading to enhanced blood coagulation [57]. Furthermore, factor V Leiden mutation, G1691A, is a single nucleotide substitution in the *F5* gene that results in reduced clearance of factor Va due to its blocked inactivation by activated protein C, increasing the risk of thrombosis [42, 57]. Also, factor XIII V34L polymorphism is a guanine to thymine substitution in exon 2 of *F13A1* that leads to a valine for leucine change in residue 34; this SNP leads to reduced susceptibility to fibrinolysis and influences fibrin degradation [57]. Moreover, MTHFR is the rate-limiting enzyme in the methyl cycle. C677T polymorphism causes a substitution of valine for alanine, resulting in a thermolabile variant of the enzyme with reduced catalytic activity; combined with the SNP AC1298C, it is associated with hyper-homocysteinemia, a risk factor for venous and arterial thrombosis [42, 58–60]. Additionally, PAI-1 is a key regulatory element in the fibrinolysis cascade, it is believed to control proteolysis and remodeling of maternal tissue during trophoblast invasion. The 4G/5G polymorphism is located 657 bp upstream from the start site of transcription within the *PAI-1* promoter and results in an allele with decreased transcriptional activity [42].

2.2.9 Trefoil factor 3 (TFF3)

TFF3 is a mucin-associated peptide co-expressed in mucus cells that acts as a mitogen to promote epithelial cell migrations and mediates epithelial repair after damage. The SNP rs11701143 is located in the promoter region of *TFF3* within the regulatory region of the transcription binding site, whereas rs225361 is an intron variant located within a regulatory region. The exact function of both SNPs remains to be elucidated [61].

2.3 Immunological factors contributing to ER

The immune system plays a major role in the process of implantation and pregnancy maintenance [62]. During decidualization, endocrine processes transform uterine fibroblasts into cells that can produce hormones, growth factors, and matrix components to support embryo implantation [63, 64]. Furthermore, tolerance of the immune maternal system is required in pregnancy to avoid rejection of the semi-allograft or allograft embryo and for its successful implantation [65]. The decidua is a privileged site for immune tolerance; a large number of molecules and immune cell types participate in this process, leukocytes, macrophages, T lymphocytes, and dendritic cells comprise around 30 to 40% of the cells within the decidual stroma in early pregnancy. Among leukocytes, uterine natural killer (uNK) cells are activated and they significantly increase during decidualization (65–70%) [66, 67]. Increases in uNK cells denote three main functions in the endometrium: regulation of placental and trophoblast growth by cytokines [68, 69], local immunomodulation [70, 71], and

control of trophoblast invasion [69]. Furthermore, trophoblast cells play a major role in immune tolerance since these cells do not express major histocompatibility complex (MHC) class I (HLA-A and HLA-B) or class II molecules; ensuring that maternal T cells with αβ receptors cannot mount a classic cytotoxic attack against fetal paternal alloantigens. The trophoblast also protects itself by expressing Fas ligand (Fas L), which is important in the elimination of maternal reactive T cells by apoptosis induction [72–74]. Other important component of this process is T-regulatory (Treg) cells; these cells are essential for immunosuppression, prevention of autoimmunity, and maternal tolerance to the fetus [75–78]. Treg cells have been shown to be locally enriched in decidua during early normal pregnancy [79]. Furthermore, Forkhead box P3 (Foxp3) is a master regulator of Treg cell development, function, and differentiation [80]. Expression of *FOXP3* was reduced approximately two-fold in endometrial biopsies of infertile women, implicating that the impaired differentiation of uterine T-cells into the Treg phenotype is a key determinant of fertility [81, 82]. On the other hand, helper T cells (CD4+) facilitate embryo implantation by regulating endometrial differentiation; they secrete interleukins and interferons that establish the implantation microenvironment. Successful pregnancy is dependent upon Th1/Th2 balance [83]. While Th1 cytokines are harmful for pregnancy, Th2 cytokines favor fetal growth and regulate uterine expression of fatty acid amide hydrolase (FAAH), LIF, and trophoblast release of human chorionic gonadotropin (hCG), which are known to play important roles during implantation [84–86]. Piccinni et al. demonstrated that T cells from decidua of women with a miscarriage show predominantly Th1-type cytokines with decreased Th2-type [84, 87, 88]. Finally, P4 and E2 mediate the downregulation of the maternal immune system [89]. P4 stimulates decidual proliferation; therefore, pregnancy results in an upregulation of P4 receptors on activated lymphocytes among placental cells and decidual CD56+ cells. In the presence of sufficient P4, these cells express progesterone-induced blocking factor (PIBF), a mediator that exerts substantial anti-abortive activities.

2.4 Biochemical markers involved in ER

We review molecular markers involved in the decidualization process that could be suitable as makers to assess ER.

2.4.1 Homeobox A10 (HOXA10)

HOXA10 is a transcription factor member of the homeobox family, known to be involved in the genetic control of embryonic development and in the regulation of the adult female reproductive tract [12, 90]. HOXA10 regulates downstream target genes that lead to endometrium development and receptivity acquisition [91], such as insulin-like growth factor binding protein 1 (*IGFBP1*) [12, 92, 93], genes of the Wnt pathway (reviewed by Sonderegger et al. [94], integrin β3 (*ITGB3*) [12, 90, 92], and empty spiracles homolog 2 (*EMX2*) [12, 95]. HOXA10 is regulated by P4 in a dose-dependent manner [12, 90, 91]. The expression of HOXA10 is low during the PP and it rapidly increases in the MSP [12, 90]. The diminished expression of HOXA10 in endometria of women with recurrent pregnancy loss (RPL) [96], adenomyosis [97], endometriosis [92], polycystic ovary syndrome (PCOS) [98], and idiopathic infertility [99] indicates that this gene could be essential for fertility [12].

2.4.2 Heparin-binding epidermal growth factor-like growth factor (HB-EGF)

HB-EGF is a member of the epidermal growth factor (EGF) family, it is expressed in the human uterus at the time of implantation and its expression is under steroidal hormone control [100–103]. The transmembrane form is associated

with cell adhesion and migration, it allows communication with the blastocyst by acting as a chemoattractant [101, 104]. HB-EGF expression is low in the PP and increases in the ESP immediately prior to the WOI, after which its levels decrease [101–103, 105]. Also, mRNA levels are low in pregnant endometrium and high in placental tissues at an early stage of development, suggesting that the HB-EGF ligand not only potentiates the health and survival of the peri-implantation embryo, but also induces the progression of its development [104]. HB-EGF stimulates epithelial expression of key endometrial proteins that are important biomarkers of the WOI, including LIF, HOXA10, and ITGB3 [100].

2.4.3 Leukemia inhibitory factor (LIF)

LIF is a member of a cytokine family with functional redundancy that includes interleukin 6 (IL6), oncostatin (OSM), ciliary neurotrophic factor (CNTF), and cardiotrophin 1 (CT1). They regulate proliferation, differentiation, and cell survival in different cellular systems [106]. LIF acts on cells by binding to the heterodimeric LIF receptor (LIFR), which consists of two transmembrane proteins, LIFR and glycoprotein 130 (gp130). LIFR activates several signaling pathways including the JAK/STAT, MAPK, and P13-kinase pathways, whereas gp130 participates in the activation of STAT1, STAT3, and STAT5B [107]. LIF induces the expression of cytokines and other regulatory molecules that could serve to regulate preimplantation development and embryo implantation [106–108]. LIF is one of the most important cytokines for receptivity during the WOI, the expression of LIF and LIFR reaches its highest level during the WOI in the MSP, LSP, and in early pregnancy in both surface and glandular epithelial cells under the influence of P4 [106, 107, 109, 110]. LIF can also be detected in decidual leukocytes, which are abundant at the implantation site; interestingly, LIF expression is low in women with unexplained infertility [106, 107, 111]. LIF also plays a crucial role in the regulation of fetal-maternal interactions during pregnancy, this cytokine mediates uterine receptivity through autocrine/paracrine interactions by binding to LIFR on the luminal epithelium to permit blastocyst attachment [106], but also regulates trophoblast function and vascular formation in the placenta [109].

2.4.4 Integrin β3 (ITGB3)

Integrins are ubiquitous cell adhesion molecules involved in maintaining normal tissue morphology and participate in cell–cell and cell-substrate interactions [100, 110, 112, 113]. In the human endometrium, integrins are involved in early embryo-endometrial interactions [90]. ITGB3 subunit is present after the ESP and its expression extend into the pregnancy [112, 114]. It has been reported that healthy fertile women show higher ITGB3 expression than patients with unexplained infertility [46, 96, 113–115]. Moreover, its dysregulation appears to characterize two distinct pathophysiological conditions that involve distinct mechanisms of defective ER: Type I and Type II. Type I defect is an out-of-phase endometrium with negative ITGB3 subunit expression, portrays a shifted WOI, and hormonal inadequacy or responsiveness is implicated, on the other hand, Type II defect is an "in-phase" endometrium with negative ITGB3 subunit expression and connotes the complete loss of the WOI. Furthermore, ITGB3 is expressed in EnSCs and endometrial glands with the highest levels in the MSP to LSP, suggesting a role in the regulation of endometrial function and implantation [115, 116]. Due to its temporal distribution and the effects of implantation when it is not present, ITGB3 is a useful molecular marker to assess ER. ITGB3 is regulated in the endometrium through a molecular mechanism via sex steroid signaling where HOXA10 acts as an intermediary [90, 96].

Other identified markers that are important for decidualization in the human endometrium include *PR*, particularly its encoded isoform progesterone receptor A (PR-A), homeobox A11 (*HOXA11*), *PTGS2*, *MUC1,* and interleukin 11 receptor (*IL11R*) [12].

2.5 Transcriptomic signature to determine the WOI

Microarray technology has been widely used to determine the transcriptomic profile of the endometrium by analyzing the expression of large batches of genes at different stages of the menstrual cycle. The most representative and commercially available test in this regard is perhaps the Endometrial Receptivity Array (ERA), developed in 2009 by Diaz-Gimeno et al., this test identifies the unique transcriptomic signature of the receptive endometrium by analyzing 238 differentially expressed genes, predicting the WOI for personalized embryo transfer (pET) [108]. Various research groups have analyzed changes in gene expression during the different phases of the endometrial cycle using microarray-based technologies [117–120], however, due to differences on results, unanimity about the main genes to be analyzed to determine the WOI has not been reached. Factors that contribute to the disagreement among studies results include differences on experimental design, utilized probes, sample acquisition day, sample size, collection method, and the application of distinct statistical analyses. Nevertheless, some genes have been reported to be expressed similarly in more than one work, here, we present a compilation of the expression profiles of those candidate genes in the human endometrium (**Table 2**).

2.6 miRNAs involved in ER

Micro-RNAs (miRNAs) are small, single-stranded, non-protein-coding RNA sequences of ~18–25 nucleotides in length that play an important post-transcriptional regulatory role in gene expression [121, 122] by targeting mRNAs for cleavage or transcriptional repression [123]. More than two decades have passed since the initial discovery of miRNAs in *Caenorhabditis elegans* by Lee et al. [124]; since then, great progress has been made in the understanding of miRNAs: what they are, how are synthesized, how regulate gene expression, and how they are involved in the formation and progression of pathological disorders. Extracellular miRNAs have been ubiquitously detected in body fluids [125]. Therefore, the presence and stability of miRNAs in biological fluids have advocated their potential as non-invasive biomarkers. Nevertheless, the identification of reliable miRNA biomarkers with reproducible profiles has been a challenge, and their diagnostic promise has remained a work in progress since they have still not entered the clinical field [126]. Nonetheless, given that miRNAs are differentially expressed in the endometrium across the menstrual cycle [127–131], several studies have been conducted to explore their role in ER [131–136]. **Table 3** presents a summary of these studies.

2.7 The endometrial secretome as a potential tool to ascertain ER

The aim to develop alternative non-invasive strategies to provide accurate receptivity assessment has drawn assiduity to the endometrial secretome, which is based in the identification of factors secreted by cells or tissues at a particular time in either physiological states or pathological conditions [137], including proteins, lipids, and metabolites. Therefore, the analysis of differentially present molecules in the uterine cavity at different time points of the menstrual cycle could potentially help to identify the WOI and to diagnose uterine pathologies. Sample collection of endometrial fluid (EF) collection in the peri-implantation period is an easy procedure performed with minimally invasive tools that could easily be implemented

Gene	Functional category	Expression profile		References
Annexin 4 [*ANX4*]	Apoptosis	PP to MSP ESP to MSP MSP to LSP	↑ ↑ ↓	[73, 86, 91–95]
Apolipoprotein D [*APOD*]	Cholesterol transport and trafficking	PP to ESP ESP to MSP	↑ ↑	[85, 92, 96]
Claudin 4 [*CLDN4*]	Cell adhesion	ESP to MSP	↑	[73, 85, 93, 94, 96, 97]
Decay-accelerated factor [DAF]	Immune modulators/ cytokines	ESP to MSP	↑	[85, 93, 94, 98]
Dickkopf-1 [*DKK1*]	Regulation of WNT signaling pathway	PP to ESP ESP to MSP ESP to LSP	↑ ↑ ↓	[73, 85, 92, 94, 96, 97, 99]
Endothelin 3 [*EDN3*]	Vasoactive substances	ESP to MSP	↓	[73, 92, 93, 100]
Growth arrest and DNA-damage-inducible protein [*GADD45*]	Cell cycle	PP to MSP ESP to MSP MSP to LSP	↑ ↑ ↑	[73, 92–94, 97, 101]
Glutathione peroxidase 3 [*GPX3*]	Response to stress and oxidoreductase activity	ESP to MSP	↑	[73, 86, 96]
Homeobox A10 [*HOXA10*]	Transcription factor	ESP to MSP MSP to LSP	↑ ↑	[55, 64, 94, 102, 103]
Inhibitor of DNA binding 4, dominant negative helix–loop helix protein [*ID4*]	Anatomical structure development	ESP to MSP	↑	[73, 92–94, 104]
Insulin-like growth factor binding protein 1 [IGFBP-1]	Anatomical structure development	ESP to MSP MSP to LSP	↑ ↑	[73, 94]
IL15 precursor [*IL15*]	Immune response	ESP to MSP	↑	[73, 85, 92–94, 96]
Mitogen-activated protein kinase kinase kinase 5 [*MAPKKK5*]	Signal transduction	PP to ESP	↑	[92, 101]
Matrix metalloproteinase 26 [*DAMMP26*]	Tissue remodeling and blastocyst invasion	MP to LPP PP to ESP MSP to LSP	↑ ↑ ↓	[87, 94] [73]
Msh homeobox homologs 1,2 [*MSX1*]	Anatomical structure development	ESP to MSP	↓	[73, 88, 91, 93, 96]
Natural cytotoxicity-triggering receptor 3 [*NCR3*]	Immune response	ESP to MSP MSP to LSP LSP to MP MP to PP	↑ ↑ ↑ ↓	[86, 87]
Olfactomedin 1 [*OLFM1*]	Anatomical structure development	PP to ESP ESP to MSP	↓ ↓	[73, 88, 92, 93]
Sex-determining region Y-box 4 [*SOX4*]	Apoptotic pathways	PP to ESP MSP to LSP MP to LPP	↓ ↑ ↑	[87, 88]
Osteopontin [*SPP1*]	Cell adhesion	PP to SP ESP to MSP	↑ ↑	[73, 85, 91–93, 96, 97, 101]
Tissue inhibitor metalloproteinase 3 [*TIMP-3*]	Degradation of the extracellular matrix	PP to ESP ESP to MSP MSP to LSP	↑ ↑ ↑	[73, 94, 95]

Genes expressed in human endometrium and its expression profiles at the different phases of the endometrial cycle. A compilation of the genes exhibiting the same expression profile in more than one work is presented, regardless of the differences among studies.

Table 2.
Expression profiles of genes involved in ER.

Reference and relevance	Methodology	Results	Targets
[132] Shows distinct miRNA profiles in LPP and MSP	**Samples:** Endometrial biopsies LPP [n = 4] and MSP [n = 4] **Technique:** Microarray Technology	49 differentially expressed miRNAs: 12 ↑ in the MSP [miR-214, 503, 134, 450, 382, 376A, 369-5p, 222, 370, 542-3p, 105, and 127] and 12 ↓ in LPP [miR-210, 193a-3p, 345, 29b, 29c, 30b, 204, 203, 582-5p, 30d, 200c, and 31]	**Predicted:** Cell cycle pathways in the LPP. Wnt signaling pathway in the PP. **Validated:** Decreased transcripts of predicted targets [cyclins, CDKs, and E2F3]
[134] Evaluates differentially expressed miRNAs in RIF-IVF patients	**Samples:** Secretory endometrium; 12 fertile women versus 11 women with RIF **Technique:** TaqMan miRNA array cards	13 differentially expressed miRNAs: 10 ↑ [miR-23b, I45, 99a, 27b, 652, 139-5p, 195, 342-3p, 150, and 374b] and 3 ↓ [miR-32, 628-5p, and 874]	**Predicted:** Wnt signaling, adherents junctions, p53 signaling, cell adhesion, and cell cycle pathways. **Validated:** Decreased transcripts of N-cadherin, H2AFX, NTN4, and SFRP4. Wnt and cell cycle pathways ↓ in RIF-IVF
[154] Makes comparison between natural vs. stimulated cycles. Suggests that ovarian stimulation may shift the WOI	**Samples:** Infertile women. Receptive [LH + 7, n = 5] vs. prereceptive [LH + 2, n = 5] in natural cycles. Receptive [hCG + 7, n = 5] vs. prereceptive [hCG + 4, n = 5] in stimulated IVF cycles **Technique:** Next-gen seq., 626 miRNAs evaluated	20 differentially expressed miRNAs in natural cycles: 8 ↑ [miR-30d, 30b, 30b, 31, 21, 193a-5p, 193a3p, 203] and 12 ↓ [miR-33a, 452, 125b, 455-3p, 455-5p, 483-5p, 143, 100, 504, 424, 424, 503]. 22 differentially expressed miRNAs in stimulated cycles: 19 ↑ [miR-187, 708, 433, 320a, 320b, 34c-5p, 320c, 320d, 485-5p, 574-5p, 375, 23b, 423-5p, 193b, 34b, 503, 424, 455-5p, 483-5p] and 3 ↓ [miR-886-5p, let-7f, let-7a]	**Predicted:** Cell cycle, transport, cell adhesion, cell death, and metabolism
[136] Provides miRNA signature of EnSCs during decidualization *in vitro*	**Samples:** Endometrial samples on oocyte retrieval day from healthy ovum donors [n = 50]. EnSCs [n = 20] isolated and cultured **Technique:** miRNA PCR array, 704 miRNAs + specific miRNA-200b primers evaluated	43 differentially expressed miRNAs: 26 ↑ [miR-95, 888, 936, 1185, 518f, 548 k, 593, 486-5p, 29c, 449b, 300, 371-5p, 1224-3p, 891a, 365, 541, 409-5p, 33b, 154, 376a, 133a, 218–2, 22, 614, 369-3p, 185] and 17 ↓ [miR-146a, 155, 181b, 181a, 135b, 181d, 200c, 141, 182, 429, 483-3p, 200a, 96, 183, 9, 30a, 126] miR-95 ↑ by P4 and E2 + P4; miR-96 and miR-135b both ↓ by E2 or P4	**Predicted:** Growth factors, interleukins, ECM remodeling enzymes. • Top pathways by ↓ miRNAs: axon guidance, adherents junction, actin cytoskeleton regulation, ErbB [EGFR] signaling, and renal cell carcinoma. • Top pathways by ↑ miRNAs: actin cytoskeleton regulation, adherent junction, axon guidance, Wnt signaling, and MAPK
[133] Provides miRNA signature of fertile human endometria: receptive vs. prereceptive	**Samples:** Receptive MSP [LH + 7, n = 4] vs. prereceptive ESP [LH + 2, n = 5] endometrial biopsies from 9 healthy fertile women **Technique:** Microarray, 723 human and 76 human viral miRNAs evaluated	4 significantly expressed different miRNAs in receptive samples: 2 ↑ [hsa-miR-30b and 30d] and 2 ↓ [hsa-miR-494 and 923] Suggests 12 genes that could serve as a new panel for ER: CAST, CFTR, DPYSL2, FI IR, FGFR2, LIF, MTFI, NPAS2, P4HA2, PPARGCIA, TACC2, RAB40B	**Predicted:** Transcription, cell proliferation, and apoptosis. Involvement in pathways such as axon guidance, Wnt/β-catenin, ERK/MAPK, TGF-β, p53 and leukocyte extravasation. They identified *SEPT7, CRMP1, SLC44A1, HES1, FXR2,* and *TNF144B* as genes that interact with genes *MIR30B* and *MIR30D*

Reference and relevance	Methodology	Results	Targets
[130] Differential miRNAs across cycle. Release of miRNAs into the EF and its uptake by the embryo	**Samples:** EF [n = 20] at different phases of the menstrual cycle of healthy women. Timing of sample collection: EPP, LPP, ESP, WOI, and LSP **Technique:** Microarray, 866 miRNAs evaluated	Compared with the WOI, 9 differentially expressed miRNAs were identified in the EPP, 8 in the LPP, 6 in the ESP and 4 in the LSP. MiR-30d was the most differentially secreted maternal miRNA in the EF during the WOI	**Predicted:** Cell cycle and endocrine processes
[135] Shows a significant different expression of miRNAs in the WOI of RIF patients that may contribute to impaired ER	**Samples:** Endometrial biopsies from the WOI [5–7 days after ovulation]: 7 from RIF group and 5 from control group [infertile patients that delivered after one transfer attempt] **Technique**: Microarray Technology	With a 2-fold threshold: 105 miRNAs were differentially expressed: 93 ↑ and 12 ↓. After raw signal value correction, 15 were found to be significantly different. 10 ↑ [hsa-miR-374a-5p, 145-5p, 30b-5p, 196b-5p, 199a-5p, 199b-5p, 449a, 424-5p, 125b-5p, 21-5p] and 5 ↓ [hsa-miR-1207-5p, 4306, 572, 5739, 6088]	**Predicted:** TAM analysis: miR-30 family, human embryonic stem cell regulation, epithelial-mesenchymal transition, and miRNA tumor suppressors. Network regulatory analysis: 176 miRNA-mRNA interactions. The top core mRNA were ABP1, AQP3, ASS1, and TIMP3, the top core miRNAs were has-miR-4668-5p, 429, and 5088

Studies conducted to analyze miRNA expression profiles during the menstrual cycle as potential biomarkers of the WOI. A summary of the differentially expressed miRNAs and predicted targets found in recent studies is presented. Its relevance regarding the role of miRNAs is also addressed.

Table 3.
Studies of miRNA-profiling during the WOI.

in ART procedures. Proteomics of EF has already rendered valuable information regarding ER; Casado-Vela et al. identified 803 proteins in EF aspirates using three different proteomic strategies [138]. Additionally, Boomsma et al. [139] analyzed endometrial secretions prior to embryo transfer from 210 women undergoing IVF to determine differences in cytokine profiling at the time of implantation, finding a negative and a positive association of monocyte chemo-attractant protein-1 (MCP-1) and IFN-γ-inducible 10 kDa protein (IP-10) levels and implantation, respectively. Lipidomics, on the other hand, seems to have rendered slight information on receptivity [140], nevertheless, a study performed by Berlanga et al. [141] and followed by Vilella et al. [142, 143] carried out lipidomic analyses of EF from patients at different stages of their menstrual cycle, they determined a significant increase in Prostaglandin E2 (PGE2) and Prostaglandin F2α (PGF2α) between days 19 and 21, coincident with the WOI. In a recent study performed by Durairaj, Aberkane et al. [144], the contribution of EnSCs to failed implantation was examined by analyzing the secretome profile of EnSCs cultures *in-vitro*. From there, they encountered that secretome profiles of pregnant women are less divergent in implantation-positive-cultures particularly in Day 0 (undifferentiated cells), suggesting that endometrial defects linked to reproductive failure could be more prominent in the PP, a phase that is commonly thought to be not relevant for ER studies. This research group also demonstrated that the secretome of undifferentiated EnSCs compromises blastocyst development. Finally, they determined that a deficiency of endometrial mesenchymal stem-like cells (MSCs) could lead to aberrant EnSC function and implantation failure. Overall, this study remarks the importance of progenitor cell populations in

the endometrium that supports the acquisition of receptivity and raises the prospect of screening the endometrium before the initiation of an ART procedure.

2.8 The microbiome as a novel aspect of ER

Historically, the uterus was assumed to be free of bacteria as the fetal environment was considered to be physiologically sterile [145], this notion implies that the neonate's microbiome is acquired only during and after birth. Although recent research still supports this conception [146], others have characterized upper genital tract microbiota [147–150], suggesting that the endometrial and vaginal microbiota not be identical [151]. What is more, the study by Moreno et al. [147, 152], which defined the microbiota in the EF as *Lactobacillus*-dominated (LD) or non-*Lactobacillus*-dominated (NLD), suggested that the presence of an NLD microbiota in a receptive endometrium was associated with a significant decrease in implantation, pregnancy, ongoing pregnancy, and live birth rates. Nevertheless, they acknowledge that in the absence of pathological signs, an NLD microbiota could be considered normal since *Lactobacillus*-deficient communities have been identified in the genital tract of otherwise healthy asymptomatic women [153]. This conception sets the stage for further research of the human microbiome, expands the possibilities to assess individualized receptivity based on the endometrial microbiome, and opens the door to explore targeted therapies for an altered endometrial microbial habitat.

3. Remarks

This review encloses different aspects of ER, spotlighting the opening of the WOI. Altogether, this compilation could aid in the development of new clinical practices that define an individual's receptive window for pET to improve ART results ultimately.

Nowadays, ER is the rate-limiting step in successful ART procedures that end up in pregnancy and child delivery. The endometrial tissue is a ponderous element in fertility; it constitutes the soil in which a viable embryo will implant to achieve progeny. The attainment of ER involves an extensive assortment of genetic and biochemical mechanisms that must integrate in a parallel manner. Understanding of this process as an entity is still insufficient; nevertheless, the surge of new technologies is contributing in the deciphering of receptivity mechanisms and in search of novel biomarkers that could serve to detect the WOI. Notably, although most studies focus on individual genetic mutations, a more comprehensive view of the parental genetics is needed to determine whether an endometrium is adequate for embryo transfer before the initiation of an ART procedure. Due to ambiguous or non-conclusive results in search of genetic predispositions of endometrial-associated infertility, it would be controversial to provide genetic counseling currently. Perhaps, in the future, massive sequencing could help to provide insights into the importance of single and multiple genetic mutations to establish a receptive or non-receptive profile. If assertive, this profile could be applied as an endometrial pre-implantation parental test to improve the rates of healthy pregnancies and live births. With this in mind, in our opinion, the best short-term approaches towards detecting or improving ER are the transcriptome, microbiome, and miRNA signatures, all achievable using the power of NGS. This review encloses different aspects of ER, spotlighting the opening of the WOI. Altogether, this compilation could aid in the development of new clinical practices that define an individual's receptive window for pET to improve ART results ultimately.

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Abbreviations and nomenclatures

3D	three-dimensional
ApoE	apolipoprotein E
ART	assisted reproductive tech
CNTF	ciliary neurotrophic factor
CT1	cardiotrophin 1
E2	estrogen
ECM	extracellular matrix
EF	endometrial fluid
EGF	epithermal growth factor
EMX2	empty spiracles homolog 2
eNOS	endometrial nitric-oxide synthase
EnSCs	endometrial stromal cells
EPP	early-proliferative phase
ER	endometrial receptivity
ERA	endometrial receptivity array
ESP	early-secretory phase
ESR1	estrogen receptor 1
F13A1	coagulation factor XIII A chain
F2	coagulation factor II
F5	coagulation factor V
F8	coagulation factor 8
FAAH	fatty acid amide hydrolase
Fas L	Fas ligand
FGB	β fibrinogen
Foxp3	Forkhead box P3
gp130	glycoprotein 130
GPIIIa	glycoprotein IIIa
HAUSP	herpesvirus-associated ubiquitin-specific protease
HB-EGF	heparin-binding epithermal growth factor-like growth factor
hCG	human chorionic gonadotropin
HOXA10	homeobox A10
HOXA11	homeobox A11
HPA1	human platelet alloantigens 1
HSCORE	histological score
IGFBP1	insulin-like growth factor binding protein 1
IL11R	interleukin 11 receptor
IL6	interleukin 6
IP-10	IFN-γ-inducible 10 kDa protein
ITGB3	integrin β3
IVF	in-vitro fertilization
LD	lactobacillus-dominated
LH	luteinizing hormone
LIF	leukemia inhibitory factor
LIFR	leukemia inhibitory factor receptor
LPP	late-proliferative phase
LSP	late-secretory phase
MCP-1	monocyte chemo-attractant protein-1
MDM2	murine double minute 2
MHC	major histocompatibility complex
MiRNA	microRNA
MP	menstrual phase

MSCs	mesenchymal stem-like cells
MSP	mid-secretory phase
MTHFR	methylenetetrahydrofolate reductase
MUC1	Mucin 1
MUC4	Mucin 4
NGS	next generation sequencing
NLD	non-lactobacillus-dominated
OSM	oncostatin
P4	progesterone
TP53	tumor protein 53
PAI-1	plasminogen activator inhibitor-1
PCOS	polycystic ovarian syndrome
PCR	polymerase chain reaction
pET	personalized embryo transfer
PGE2	prostaglandin E2
PGF2α	prostaglandin F2α
PGs	prostaglandins
PIBF	progesterone-induced blocking factor
PP	proliferative phase
PR	progesterone receptor
PR-A	progesterone receptor A
RIF	repeated implantation failure
RPL	recurrent pregnancy loss
RSA	recurrent spontaneous abortion
SNP	single-nucleotide polymorphism
SP	secretory phase
TAM	tool annotations human miRNAs
TFF3	trefoil factor 3
Treg	T-regulatory cells
uNK	uterine natural killer
VEGF	vascular endothelial growth factor
VNTR	variable number tandem repeats
WOI	window of implantation

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