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Endometrial Receptivity: An Integrated Evaluation of Genetic, Epigenetic and Artificial Intelligence-Assisted Diagnostic Approaches

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Abstract

Endometrial receptivity plays a key role in successful embryo implantation and is regulated by a combination of genetic and epigenetic mechanisms. This review aims to provide an overview of these regulatory processes and to highlight their relevance in clinical practice. In addition, current genomics-based diagnostic methods and emerging artificial intelligence-assisted approaches are discussed in relation to their potential use in evaluating endometrial receptivity. A literature review was conducted using the Scopus, PubMed, Dergipark, Web of Science, and national thesis databases, including peer-reviewed articles and systematic reviews published between 2000 and 2025. Key molecular components such as gene expression patterns, DNA methylation, and non-coding RNAs were evaluated together with available clinical validation data.

The findings indicate that endometrial receptivity is associated with the regulated expression of genes such as HOXA10, LIF, and integrin αvβ3, supported by epigenetic mechanisms including DNA methylation and miRNAs. Molecular diagnostic tools such as ERA and beREADY may help identify the individual implantation window. In addition, artificial intelligence-based models may support the integration of complex molecular data and contribute to clinical decision-making.

Overall, understanding endometrial receptivity through genetic and epigenetic perspectives may help improve prediction and support personalized approaches in assisted reproductive technologies. With ongoing technological developments, these approaches may become increasingly relevant in infertility management.

Keywords: Endometrial Receptivity; Epigenetics; Implantation Failure; Assisted Reproductive Technologies; Artificial Intelligence

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What is Endometrial Receptivity?

Endometrial receptivity is a state of biological suitability that occurs within a limited time frame and is required for an embryo to successfully implant into the endometrium. This condition depends on a complex and multilevel molecular communication network between the embryo and the endometrium. The scientific basis of this concept was established by Noyes and colleagues, who studied the morphological changes of the endometrium throughout the menstrual cycle in 1975 [1]. The concept was first used in 1993 by Christopher R. Murphy in relation to changes in the surface membranes of uterine epithelial cells during the pre-implantation period [2], and in his subsequent study the following year, these changes were termed "plasma membrane transformation" [3]. Since the 1990s, surface structures known as pinopodes have been investigated for their correlation with the implantation window. The presence of pinopodes has been found to be associated with implantation and pregnancy rates in IVF patients and is still considered a reliable marker of receptivity today.

From a physiological perspective, endometrial receptivity occurs during the mid-menstrual cycle, in the period following ovulation known as the "implantation window (window of implantation, WOI)," which lasts approximately 4 to 5 days. During this time, the endometrium becomes ready to accept the embryo at histological, biochemical, and molecular levels.

A major Cause of Pregnancy Failure

In humans, the implantation rate per natural cycle remains limited to approximately 30%, and the frequent occurrence of repeated failed transfers despite high-quality embryos in assisted reproductive technologies demonstrates the critical role of endometrial factors in pregnancy

success. In the literature, it has been reported that insufficient endometrial receptivity may be one of the main underlying causes in approximately 30% of unexplained infertility cases [4]. Particularly in cases diagnosed with recurrent implantation failure, the endometrium is thought to lack molecular suitability, independent of embryo quality. Endometrial receptivity is not a process controlled solely by hormonal regulation; rather, it is the result of a complex regulatory network at both genetic and epigenetic levels. In this process, the temporally specific upregulation or downregulation of many genes, including HOXA10, LIF, MUC1, integrin avß3, VEGF, and osteopontin (SPP1), plays a decisive role. In recent years, diagnostic methods based on the evaluation of the expression profiles of these genes have been developed, and molecular tests such as ERA (Endometrial Receptivity Array), WinTest, and beREADY have entered clinical practice [5].

In addition to genetic structure, epigenetic mechanisms that control gene expression also have a significant impact on receptivity. DNA methylation, histone modifications, and non-coding RNAs (particularly microRNAs and long non-coding RNAs) play a role in regulating the temporally specific expression of relevant genes. Disruption of these epigenetic regulators may negatively affect embryo-endometrium synchronization, leading to implantation failures. Today, advances in molecular biology have enabled the identification of meaningful biomarkers for clinical practice through high-volume genomic, transcriptomic, and epigenetic data. The analysis of these data and their integration into clinical decision-making processes increasingly rely on Artificial Intelligence (AI), Machine Learning (ML), and bioinformatic algorithms. In particular, the analysis of RNA data obtained from endometrial biopsies using Al models enables individual-level determination of the implantation window, personalization of treatment planning, and may contribute to improved clinical decision-making. In addition, AI supported classifications in imaging-based systems such as digital pathology provide more objective and standardized analyses of receptivity at cellular and tissue levels.

Aim and Scope of the Review

The aim of this review is to systematically examine the genetic and epigenetic regulatory mechanisms related to endometrial receptivity and to address advanced diagnostic approaches and next-generation technologies, particularly artificial intelligence-based systems, in a holistic manner in line with the current literature. The objective is to contribute to the development of more effective, individualized, and scientifically grounded approaches in clinical practice by revealing the multilayered nature of this complex process.

Genetic Basis of Endometrial Receptivity

Endometrial receptivity is a timing-sensitive process governed by a complex genetic network. The correct expression of the genes involved, at the appropriate time and level, is critical for successful implantation. Numerous events, including embryo attachment to the endometrium, differentiation of endometrial stromal cells, remodelling of the extracellular matrix, regulation of immune system cells, and balanced cytokine secretion, are controlled at the genetic level.

HOXA10 and HOXA11

HOX genes are evolutionarily conserved transcription factors involved in embryonic development and tissue differentiation. In particular, HOXA10 and HOXA11 exhibit increased expression in the uterine endometrium throughout the receptivity period. The upregulation of these genes during the secretory phase is associated with the endometrium becoming ready to accept the embryo. HOXA10 also upregulates other genes directly related to receptivity, such as β3 integrin, IGFBP-1, and LIF. Hypomethylation or mutations of HOXA10 have been associated with infertility, and low expression levels have been detected particularly in cases of recurrent implantation failure [6].

LIF (Leukemia Inhibitory Factor)

LIF is a cytokine belonging to the interleukin-6 family and plays a central role in embryoendometrium interaction. LIF is the most pleiotropic member of the interleukin-6 family and regulates cell proliferation, differentiation, and survival through pathways such as JAK/STAT, MAPK, and PI3K [7]. It may exert opposing effects in different cell types; for example, it can stimulate growth in some cells while inhibiting it in others [8]. LIF enhances the embryo's ability to attach to the endometrium, supports the decidualization of stromal cells, and contributes to the regulation of the endometrial immune microenvironment. It is essential for embryo implantation, placental formation, and nervous system development. In addition, it is used in the self-renewal of embryonic stem cells [9]. In the absence of LIF, implantation may fail to occur.

Integrins

Integrins are transmembrane receptors involved in cell-cell and Cell-Extracellular Matrix (ECM) interactions. The avß3 integrin is upregulated in the luminal epithelium during the receptivity period and facilitates adhesion between the trophectoderm layer of the embryo and the endometrium. Recurrent implantation failure and infertility have been associated with high integrin ß3 levels caused by endometrial copy number variation. Reduced ß3 integrin levels are considered a molecular indicator of endometrial dysfunction [10].

MUC1 (Mucin 1)

MUC1 is a glycoprotein, cell surface-associated anti-adhesive molecule. Regulation of MUC1 expression during the secretory phase is important for embryo selectivity. Interestingly, high MUC1 levels create a barrier against the embryo, whereas locally reduced MUC1 expression at the implantation site allows adhesion.

Therefore, MUC1 is a molecule that is selectively regulated at the microenvironmental level during the receptivity period. In a study conducted in mice, it was shown that estrogen-induced proline-rich acidic protein 1 (Prap1) increased Mucin 1 (Mucl) expression and negatively affected embryo adhesion [11]. The same study found that Prap1 increased particularly at high estrogen levels and decreased during the implantation period. Overproduction of Prapl in endometrial epithelial cells upregulates Mucl and extracellular matrix-related genes, thereby reducing embryo adhesion. These findings highlight the importance of estrogen-mediated genetic regulation in the implantation process.

VEGF (Vascular Endothelial Growth Factor)

The increased vascularization and angiogenesis that occur in the endometrium during implantation are mediated by VEGF. VEGF is an important factor that not only promotes new blood vessel formation but also supports molecular communication between the embryo and the endometrium. By enhancing endometrial receptivity, it facilitates the implantation process. Increased VEGF expression contributes to the development of spiral arteries in the endometrium and to the establishment of the vascular environment required for

embryo nourishment. In addition, VEGF is active in stromal cell signalling pathways that support receptivity. Recent studies indicate that disruption of VEGF levels may be associated with recurrent implantation failure and miscarriages. Therefore, balanced expression of VEGF is considered critical for successful implantation [12].

Osteopontin (SPP1)

SPP1 is one of the glycoproteins that increase in the endometrium during the secretory phase. It facilitates embryo adhesion and interacts strongly with integrin avß3. In infertility cases where SPP1 expression is reduced, the endometrial matrix is thought to create an unfavorable microenvironment for the embryo. In a study evaluating whether osteopontin levels could be used as a biomarker in the diagnosis of endometriosis, plasma and peritoneal fluid samples were analyzed. However, the data revealed that osteopontin levels were not significantly associated with either the presence or the stage of the disease [13]. Therefore, osteopontin is not currently considered a reliable diagnostic marker.

Clinical Implications

The lack of coordinated expression of these genes during the receptivity period may prevent successful embryo attachment. Significant decreases in HOXA10, LIF, and integrin expression have been reported in cases of recurrent implantation failure [14]. The molecular analysis of genetic expression profiles has enabled personalized timing of embryo transfer. Therefore, genetic-level analysis of receptivity has become an important tool for increasing clinical success.

Epigenetic Regulators in Endometrial Receptivity

Although endometrial receptivity is a complex biological process under genetic control, the fundamental element that ensures the temporal and tissue-specific precision of this genetic regulation is epigenetic regulatory mechanisms. Epigenetics refers to the regulation of gene expression without any change in the DNA sequence. This regulation is achieved through various molecular mechanisms, primarily DNA methylation, histone modifications, and noncoding RNAs (miRNAs, IncRNAs) [15]. In the endometrium, the balance of these mechanisms is critical for the formation of a microenvironment suitable for implantation. In several translational studies using human endometrial tissue and trophoblast cell lines as direct experimental models in implantation research related to successful pregnancy, abnormal miRNA profiles associated with low receptivity in the human endometrium demonstrated that epigenetic regulation is also effective at the post-transcriptional level [16]. In particular, it has been shown that the expression of genes directly related to receptivity, such as LIF (Leukemia Inhibitory Factor), HOXA10, and members of the integrin family, increases under progesterone stimulation. To demonstrate the involvement of epigenetic mechanisms in the regulation of these genes, in vitro models using DNA methyltransferase inhibitors have been employed, and these inhibitors were experimentally shown to significantly increase HOXA10 expression. This finding indicates that methylated promoter regions play an active role in silencing genes that contribute to receptivity [17]. Similarly, histone acetylation has been identified as a determinant of the expression of implantation-related genes, and increased expression levels of receptivity-associated genes have been reported in endometrial stromal cells treated with histone deacetylase inhibitors (e.g., Trichostatin A) [18]. These results demonstrate that epigenetic modifications constitute a fundamental biological tool in determining the functional state of the endometrium.

In conclusion, studies have shown that a successful implantation process is possible not only through the correct timing and dosage of hormonal signals but also through the conversion of these signals into cellular functions *via* epigenetic pathways [16]. Epigenetic mechanisms such as DNA methylation, histone modifications, and miRNA-mediated translational regulation form the molecular basis that determines the capacity of endometrial cells to recognize, attach to, and support the embryo. Therefore, targeting epigenetic regulators in both diagnostic and therapeutic strategies may enable the development of new approaches to increase clinical success in cases of recurrent implantation failure or unexplained infertility. Identification of epigenetic alterations through non-invasive biomarkers may also play an important role in determining personalized implantation timing.

DNA Methylation

DNA methylation occurs through the addition of a methyl group to the 5-carbon of cytosine bases and generally leads to repression of gene expression in promoter regions. In endometrial tissue, methylation profiles that vary throughout the menstrual cycle have been observed. During the secretory phase, hypomethylation of certain genes (e.g., HOXA10, LIF) increases their expression and contributes to receptivity, whereas hypermethylation of some antiadhesion genes suppresses their expression, thereby facilitating embryo attachment [14]. In particular, DNMT (DNA methyltransferase) enzymes play a role in establishing methylation patterns. Studies have shown that DNMT1 and DNMT3B exhibit cyclical expression in the endometrium and that their expression levels change during the receptive period [19]. Abnormal methylation profiles have been associated with implantation failure.

Histone Modifications

The addition of groups such as acetyl, methyl, phosphate, and ubiquitin to histone proteins leads to relaxation or condensation of chromatin structure. In particular, acetylation of histones H3 and H4 has a facilitating effect on gene expression. During the receptivity period, histone acetylation has generally been found to increase in the promoter regions of genes involved in adhesion and implantation, whereas methylation is elevated in genes that suppress immune activity [5]. HDAC (histone deacetylase) enzymes remove acetyl groups from histones, leading to gene silencing. Increased HDAC activity in non-receptive endometrium may prevent the expression of appropriate genes.

Non-Coding RNAs (miRNAs and IncRNAs)

Non-coding RNAs (ncRNAs) are transcriptional elements that do not encode proteins but play fundamental roles in the regulation of gene expression at post-transcriptional and epigenetic levels. In the investigation of complex biological events such as endometrial receptivity, ncRNAs - particularly the microRNA (miRNA) and long non-coding RNA (IncRNA) subgroups - have become prominent.

miRNAs are small ncRNAs approximately 21-25 nucleotides in length that mediate gene silencing by base-pairing with target mRNAs. In endometrial tissue, miRNA expression profiles that differ specifically during the receptivity period play an effective role in regulating cellular and molecular processes critical for successful embryo implantation [5]. For example, miRNAs such as miR-145, miR-223, and miR-31 have been shown to be expressed in the endometrium during the implantation window and to directly

influence implantation by targeting cell adhesion molecules, cytokine receptors, and genes involved in steroid hormone signaling pathways [20]. These miRNAs function by suppressing or activating, at the translational level, implantation-related genes such as LIF, HOXA10, and ITGAV [45]. The miR-200 family, in particular, plays a critical role in Epithelial-Mesenchymal Transition (EMT) processes and in regulating the expression of cell-cell adhesion molecules such as E-Cadherin (CDH1). Reduced miR-200 expression in endometrial epithelial cells may disrupt interactions with stromal cells, thereby impairing receptivity [21]. In addition, miRNAs indirectly contribute to progesterone receptor regulation, immune tolerance mechanisms, and stromal decidualization processes. On the other hand, long non-coding RNAs (IncRNAs), which are generally longer than 200 nucleotides, are involved in transcriptional regulation, chromatin remodelling, and stabilization of epigenetic memory. These molecules interact with epigenetic regulatory proteins (e.g., Polycomb Repressive Complex 2 - PRC2) to direct histone modifications at the promoter regions of target genes [22]. The IncRNA H19, expressed in the endometrium, has been found to be particularly effective in cell proliferation, stromal cell differentiation, and immune modulation. Some studies suggest that H19 may enhance implantation competence in endometrial cells by modulating IGF2 gene expression [23]. These molecular-level regulatory mechanisms not only determine the capacity of the endometrial environment to accept the embryo but are also considered potential biomarkers for the molecular diagnosis of recurrent implantation failure cases.

Clinical Implications and the Impact of Epigenetic Disorders

Disruptions in the epigenetic profile may confer an inappropriate "epigenetic signature" on endometrial tissue. As a result, the endometrium may appear morphologically receptive while remaining molecularly unsuitable for implantation. Studies have shown that in cases of recurrent implantation failure, HOXA10 is hypermethylated and that increased methylation in the promoter region of LIF leads to suppressed expression [24]. In addition, among recently developed diagnostic methods, the detection of epigenetic signatures is gaining increasing importance. In this way, receptivity disorders that cannot be identified by classical histological evaluations can be revealed through epigenetic analyses.

Genomics-Based Diagnostic Methods: Transcriptomic Evaluation of Endometrial Receptivity

For many years, diagnostic assessments of endometrial receptivity have been based on histological criteria and hormonal timing. However, these conventional methods fall short in evaluating synchronization at the molecular level. As a result, endometria that appear morphologically normal but are molecularly non-receptive are often overlooked. Therefore, in recent years, highly sensitive genomics-based diagnostic methods that assess receptivity through transcriptome analysis have been developed. These tests aim to determine the individual-specific "window of implantation" by analyzing RNA expression profiles obtained from endometrial biopsies.

Endometrial Receptivity Array (ERA)

One of the most widely used tests developed to objectively and molecularly assess endometrial receptivity is the Endometrial Receptivity Array (ERA), which was introduced in 2009 by DíazGimeno and colleagues. The ERA test evaluates the expression profile of 248 genes associated with receptivity to determine whether the endometrium is suitable for embryo transfer [25]. RNA samples obtained via biopsy are analyzed using microarray or Next-Generation Sequencing (NGS) techniques. Based on this analysis, endometrial tissue is classified as "receptive," "prereceptive," or "post-receptive".

The ERA test provides diagnostic value particularly in cases of recurrent implantation failure and unexplained infertility. When embryo-endometrium synchronization is disrupted, it becomes possible to reschedule embryo transfer according to the "personal receptivity time" determined by the ERA test. This personalized approach, referred to in the literature as Personalized Embryo Transfer, has the potential to significantly increase pregnancy rates [26]. The main strength of the ERA test lies in enabling individualized embryo transfer timing at the molecular level. However, the test also has certain limitations. For instance, it does not directly measure epigenetic regulation; rather, it offers a window only at the transcriptomic level. Therefore, future tests that more comprehensively evaluate ncRNAs and epigenetic modifications further may improve the accuracy of ERA. In conclusion, the regulatory role of non-coding RNAs in endometrial receptivity remains an important area of research for improving implantation success. The use of these molecules as diagnostic biomarkers may have a transformative impact, particularly in personalized treatment approaches.

beREADY Test

beREADY is another molecular test based on endometrial transcriptome analysis that operates on a principle similar to ERA. Unlike ERA, the analyzed gene set is narrower; however, the use of specific algorithms allows for faster results. It has been developed as an alternative to ERA through artificial intelligence-assisted analysis models and rapid library preparation techniques. With the beREADY test, receptivity status is similarly categorized as "receptive," "prereceptive," or "post-receptive". In addition, beREADY aims to evaluate receptivity together with inflammatory gene profiles in certain cases.

Win-Test and Other Diagnostic Alternatives

Win-Test is an alternative to tests such as ERA and beREADY and is primarily applied in Spain. It is essentially based on RT-qPCR-based gene expression analysis and evaluates receptivity using a limited number of "key genes". In addition to these tests, some centers perform similar receptivity assessments using custom-developed panels or RNA-seq analyses. However, most of these tests have not yet been widely adopted in clinical practice due to the lack of large databases and standardized validation processes.

Advantages and Limitations of Genomic Tests

Currently, genomic tests used to assess endometrial receptivity provide significant contributions to personalized medicine applications in the diagnosis and treatment of female infertility. The main advantages of these tests include their ability to perform molecular-level evaluations, their higher sensitivity and specificity compared with classical histological assessments, and the possibility of individualized embryo transfer timing [25]. The ERA test, in particular, analyzes the expression profile of 248 genes at the transcriptomic level to define whether endometrial tissue is "receptive," thereby enabling personalized embryo transfer timing. This offers clinical benefit, especially for patients experiencing recurrent implantation failure.

Another important advantage of genomic tests is that they allow the combined evaluation of genetic, epigenetic, and transcriptomic data. In this way, information can be obtained not only about the receptivity window but also about the immunological status of the endometrial tissue, stromal cell differentiation, and intercellular signalling pathways [5]. This multidisciplinary approach provides a foundation for developing patient-specific treatment plans.

Despite these advantages, genomic tests also have certain limitations. First, the cost of these tests is relatively high, which restricts their widespread clinical use [27]. The reliability of test results is highly dependent on biopsy timing, sampling techniques, and laboratory conditions. In addition, there is still no standardized protocol for the interpretation of genomic data, and differences in interpretation may arise between analyses conducted at different centers [28]. Moreover, the classification of receptivity as "receptive," "pre-receptive," or "post-receptive" carries the risk of reducing receptivity to a simplified outcome rather than reflecting it as a multidimensional biological process. Consequently, the complex nature of embryo-endometrium interaction may not be fully captured. Furthermore, some meta-analyses have reported that evidence demonstrating a significant increase in pregnancy rates with tests such as ERA remains limited, and additional randomized controlled studies are needed. In conclusion, although genomic tests are valuable tools for understanding and managing endometrial receptivity, careful patient selection and interpretation are required in light of existing limitations and ongoing debates.

Clinical Impact and Evidence from the Literature

The clinical use of the Endometrial Receptivity Array (ERA) test has attracted attention due to its potential to improve pregnancy outcomes by enabling individualized embryo transfer timing, particularly in patients with a history of Recurrent Implantation Failure (RIF). In this context, multicenter randomized controlled studies on Personalized Embryo Transfer (PET) strategies have shown that correcting transfer timing in individuals who undergo transfer outside the Window of Implantation (WOI) can significantly increase clinical pregnancy rates [29]. For example, studies conducted by Diaz-Gimeno and colleagues demonstrated that by identifying non-receptive patients using the ERA test and rescheduling transfer timing, increases in live birth rates were achieved [25]. However, some studies evaluating the routine use of the ERA test in young patients with a good prognosis have reported that the test does not significantly increase pregnancy rates [30]. These conflicting results have been attributed to genetic and physiological differences among patients, as well as variability in the algorithms used to interpret test results. In addition, factors such as endometrial biopsy timing, cyclical variations, and the reproducibility of test results may also influence clinical outcomes [27]. Indeed, some researchers emphasize that the molecular profile provided by the ERA test alone may be insufficient to predict clinical success and should instead be evaluated together with factors such as the endometrial microenvironment, immune responses, and embryo quality [5]. In this regard, the clinical impact of the ERA test is directly related to appropriate patient selection, precision in the application protocol, and multidisciplinary evaluation of the results. At present, larger randomized studies with long-term follow-up are needed to expand the use of personalized transfer strategies.

Next-Generation Approaches: Artificial Intelligence and Bioinformatics in Endometrial Receptivity

Advances achieved in understanding endometrial receptivity at the genetic, transcriptomic, and epigenetic levels have enabled a more in-depth elucidation of these complex biological processes. Particularly in recent years, developments in digital technologies and computational biology have come to the forefront, allowing the integration of high-volume "-omics" data (e.g., genome, transcriptome, epigenome) into clinical practice. This transformation has rendered classical diagnostic approaches at the molecular level insufficient. Indeed, such data are characterized by both high dimensionality and high heterogeneity, making their analysis largely infeasible using manual or traditional parametric statistical methods [31]. For this reason, Artificial Intelligence (AI)-based techniques such as Machine Learning (ML), deep learning, and data mining are assuming an increasingly central role in endometrial receptivity analyses. These technologies contribute not only to the processing of large datasets but also to diagnostic modelling, pattern recognition processes, and the determination of individualized treatment strategies. Particularly at the transcriptomic level, algorithms that enable the simultaneous analysis of thousands of genes facilitate the identification of specific molecular signatures (gene signatures) and the construction of patient-specific receptivity profiles [25].

For example, the analysis of gene expression data obtained from endometrial biopsies through classification algorithms (Random Forest, Support Vector Machines, XGBoost) or dimensionality reduction methods (PCA, t-SNE) has made it possible to predict the window of implantation at an individual level with high accuracy [32]. When integrated into clinical decision support systems, these approaches allow the development of far more rational, effective, and cost-efficient treatment plans compared with empirical practices. In conclusion, the convergence of bioinformatics, computational genomics, and Al-supported decision systems in endometrial receptivity analysis is fundamentally transforming both diagnostic processes and treatment planning, accelerating the integration of molecular medicine into personalized reproductive health. As this integration continues to strengthen, diagnostic and therapeutic approaches for multifactorial conditions such as implantation failure are expected to become more targeted.

Analysis of Gene Expression Data Using Machine

Learning Gene expression data obtained from biopsy samples used in the assessment of endometrial receptivity were traditionally evaluated using limited analytical approaches based on fixed threshold values (e.g., up- or down-regulation of specific genes). Today, however, these methods are being replaced by Machine Learning (ML) algorithms that offer more sophisticated and individualized analytical capacity. Particularly in transcriptomics-based tests such as the ERA (Endometrial Receptivity Analysis), these data analysis approaches are integrated into both classification and exploratory analysis processes [25].

In this context, supervised learning algorithms such as Support Vector Machines (SVM), Random Forest, and XGBoost are used to classify endometrial samples into categories such as receptive, pre-receptive, or post-receptive, enabling the determination of an individual's implantation window with high accuracy. These methods also contribute to the development of decision support systems for personalized embryo transfer timing by generating predictive models

based on new patient data [32]. On the other hand, unsupervised learning techniques such as k-means and hierarchical clustering create natural groupings by considering similarities among samples, allowing the identification of potential sub-phenotypes. These techniques are particularly useful for understanding the heterogeneity of the endometrial receptivity process and for uncovering previously unrecognized molecular patterns [25]. In addition, dimensionality reduction methods such as Principal Component Analysis (PCA) and t-distributed Stochastic Neighbor Embedding (t-SNE) enable the visualization of high-dimensional gene expression data and facilitate clearer analysis of inter-sample differences. In this way, it becomes possible to develop diagnostic panels based on a smaller number of biologically meaningful genes. Indeed, the 248-gene panel used in the first-generation ERA test has begun to give way to more compact panels that provide comparable diagnostic sensitivity. In next-generation studies, efforts to develop faster, lower cost, and more practical tests based on a reduced number of target genes (e.g., 40-50 genes) are increasing [33]. These developments not only enhance clinical efficiency but also expand the accessibility of diagnostic processes.

In conclusion, the use of machine learning algorithms in endometrial receptivity analysis significantly increases diagnostic accuracy and clinical predictive power, while also laying the groundwork for the discovery of novel molecular biomarkers. This technological transformation is regarded as one of the cornerstones of personalized reproductive treatments.

Digital Pathology and Image Analytics

Artificial Intelligence (AI)-based applications in reproductive biology are not limited to genetic and transcriptomic analyses; they also enable a more objective and quantitative evaluation of histological data. In particular, AI-assisted image analysis is gaining increasing prominence as a means to overcome the subjective limitations of classical pathological evaluation methods in detecting micromorphological changes associated with endometrial receptivity. In this context, tissue sections obtained from endometrial biopsy samples are converted into high-resolution digital formats using Whole Slide Imaging (WSI) technologies, and these images are analyzed using deep learning models such as Convolutional Neural Networks (CNNs) [34]. Through such analyses, various histomorphological parameters including the organization of glandular structures, stromal cell density, degree of edema, vascularization patterns, and immune cell infiltration can be evaluated in a quantitative and standardized manner independent of human observation. These computational pathology approaches go beyond historical classifications such as the Noyes criteria, enabling the creation of "digital tissue signatures" that reflect specific functional states of the tissue [35].

These digital signatures not only objectify morphological changes at the tissue level but also contribute to the more sensitive and reproducible identification of clinically critical parameters such as the timing and quality of endometrial receptivity. In particular, the algorithmic classification of samples corresponding to different phases of the menstrual cycle suggests that the window of implantation can be defined using AI-based approaches. By minimizing interpretation-based variability among pathologists, this approach supports the development of more reliable and personalized clinical decision support systems [36]. In conclusion, deep learning-based Al systems process morphological data related to endometrial tissue with high accuracy, enhancing diagnostic precision while complementing molecular receptivity analyses. These advances indicate that, in the future, diagnostic processes for receptivity will become digital and automated not only at the genetic level but also at the histological level.

Clinical Decision Support Systems (CDSS) and Applications

Al-supported clinical decision support systems (Clinical Decision Support Systems, CDSS) play a significant role in personalized infertility treatment. These systems can integrate multiple datasets such as patient age, hormonal profile, embryo quality, previous cycle data, and endometrial receptivity test results to provide clinicians with recommendations regarding embryo transfer timing, cycle type, and treatment protocols [37]. Particularly in integrated systems, more accurate embryo transfer decisions can be achieved by jointly analyzing ERA test results with ultrasound findings and hormone levels.

Clinical Implications and Future Perspectives

Elucidation of the molecular and epigenetic foundations of endometrial receptivity has paved the way for a paradigmatic shift in infertility treatments. In assisted reproductive technologies, particularly in cases such as recurrent implantation failure and unexplained infertility, evaluation of the endometrium, beyond embryo quality, has become imperative. In this context, accurate determination of endometrial receptivity represents a critical step for increasing pregnancy rates, preventing unnecessary embryo transfers, and implementing personalized treatment plans.

Use of Endometrial Receptivity Tests in Clinical Practice

Transcriptomics-based tests such as ERA, beREADY, and similar approaches enable the determination of endometrial receptivity timing at the individual level. By identifying the period during which the endometrium is most suitable for implantation at the molecular level, these tests make it possible to develop personalized treatment strategies that go beyond conventional embryo transfer protocols. Personalized embryo transfer developed in this direction has been shown to provide a significant increase in pregnancy rates, particularly in patients with a history of recurrent implantation failure [29].

Clinical observations indicate that receptivity cannot be reduced to a fixed time window for every individual and may even vary between different menstrual cycles in the same patient [26]. This suggests that classical "fixed-timing" embryo transfer approaches may be insufficient and that timing errors may contribute to treatment failure. In this regard, transcriptomic tests that reveal the molecular signature of the endometrium may improve clinical outcomes by dynamically matching the transfer day with the receptivity window. Moreover, the development of personalized treatment protocols based on genetically and epigenetically defined markers offers higher success rates compared with empirical, trial and error approaches [25]. Especially in cases where implantation failure is associated with the receptivity window, embryo transfers performed without molecular analysis not only reduce treatment efficacy but also lead to time loss for the patient and unnecessary costs for the healthcare system. Therefore, in cases where transferred embryos fail to implant after several IVF treatment cycles, integrating molecular receptivity tests into the diagnostic process can optimize embryo transfer timing, thereby increase clinical pregnancy rates and contribute to the rationalization of treatment strategies. Current evidence supports that

this approach may be particularly effective in resolving implantation problems related to endometrial factors [38].

Approach to Unexplained Infertility and Recurrent Implantation Failure

Unexplained Infertility (UI) is defined as the inability to achieve pregnancy despite normal findings in standard evaluation criteria, including the presence of ovulation, normal sperm parameters, and tubal patency. In this patient group, it is thought that certain molecular-level endometrial abnormalities not detectable by classical diagnostic approaches may contribute to implantation failure [39].

Recent studies have demonstrated that alterations in gene expression affecting endometrial receptivity, epigenetic modifications, and microscopic disruptions in cellular communication may play an important role in cases of unexplained infertility. In this context, irregularities detected in the expression levels of various genes that facilitate implantation may functionally impair the capacity of the endometrial microenvironment to accept the embryo. For example, decreased expression of the Leukemia Inhibitory Factor (LIF) gene - considered one of the key markers of endometrial receptivity and playing a crucial role in embryo-endometrium interaction - has been associated with implantation failure [40]. Similarly, hypermethylation of the HOXA10 gene may suppress its expression, adversely affecting endometrial stromal cell differentiation and the decidualization process [41]. In addition, alterations in receptivity-associated microRNA profiles may disrupt translational regulatory mechanisms, thereby preventing successful embryo attachment to the endometrium [5].

The frequent observation of these molecular abnormalities in patients with unexplained infertility has necessitated moving beyond classical diagnostic methods and employing more advanced diagnostic tools. Accordingly, it is recommended that tests evaluating endometrial receptivity at the molecular level (e.g., transcriptomic analyses or epigenetic panels) be integrated into diagnostic and treatment algorithms, particularly for patients diagnosed with unexplained infertility or recurrent implantation failure. By assisting in the identification of the patient-specific implantation window, these tests optimize embryo transfer timing and hold the potential to increase treatment success [29].

Guidelines, Levels of Evidence, and Practical Limitations

The role of molecular receptivity tests in clinical practice has not yet achieved a definitive recommendation standard at the international level. In guidelines published by leading organizations such as the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), recommendations regarding these tests remain limited and are generally expressed as "applicable but not strongly supported by evidence" [42]. One of the main reasons for this is that these tests have not yet been sufficiently validated in terms of efficacy and reliability through a large number of randomized controlled clinical studies with broad sample sizes [39, 43]. Although methods such as the ERA test are suggested to contribute to personalized embryo transfer, results are often derived from heterogeneous patient groups, limiting generalizability.

Another important limitation is the lack of methodological concordance among different molecular receptivity tests. Differences in biological sample types, gene expression panels, timing, and analytical algorithms constitute significant barriers to standardization in clinical interpretation. Furthermore, several studies have reported that the clinical effectiveness of these tests is not consistent across all patient groups and that they do not demonstrate significant benefit, particularly in good-prognosis cases [25]. This delays their widespread and universal clinical implementation. Nevertheless, an increasing number of multicentre and prospective studies published after 2020 indicate that personalized embryo transfer practices exert positive effects on pregnancy and live birth rates, particularly in patient groups with a history of recurrent implantation failure [33]. These findings suggest that integrating receptivity tests into clinical decision-making processes may be beneficial, especially in selected patient populations.

It is anticipated that these preliminary findings may, in the future, enable a more structured integration of molecular receptivity analyses into algorithmic clinical guidelines. To achieve this, stronger evidence supporting both the analytical validity and clinical utility of these tests is required. In addition, factors such as implementation costs, the development of patient friendly methods, and the automation of data interpretation processes will play a crucial role in determining the future prevalence of these tests.

Future Perspective: Holistic and Personalized Reproductive Medicine

Molecular receptivity analyses are expected to become increasingly sophisticated in the coming years through the integration of multilayered biological data. The combined evaluation of data obtained at the genomic, epigenomic, transcriptomic, and proteomic levels will enable a more holistic understanding of the endometrial microenvironment. In particular, the "multi-omics" approach will allow individual differences to be distinguished, making it possible to determine the implantation window with greater precision. Studies conducted in this context are focusing on integrating -omic layers to improve the diagnostic accuracy of tests that assess receptivity based on endometrial transcriptomic profiles (e.g., the ERA test) [25, 29].

Accurate and rapid analysis of such large datasets increasingly requires the use of artificial intelligence-based algorithms. Machine learning and deep learning approaches contribute to the development of personalized decision support systems by enabling the combined evaluation of molecular data obtained from endometrial biopsies or liquid samples alongside clinical data. Systems developed in this context are not limited to identifying the implantation window; they also generate predictive models aimed at defining the underlying causes of recurrent failed embryo transfers [27].

Moreover, with the advancement of minimally invasive methods, less traumatic and more repeatable alternatives to classical endometrial biopsy are gaining prominence. A growing number of recent studies indicate that uterine fluid samples or endometrial "liquid biopsy" approaches have the potential to provide molecular-level information [44]. This approach may render receptivity assessment more patient-friendly, particularly in the pre-embryo transfer period. In the future, dynamic and real-time monitoring of the implantation window may also become feasible. To this end, ongoing studies are focused on identifying biomarkers that vary throughout the cycle and can be monitored in circulation. Validation of such biomarkers is of great importance not only for diagnosis but also for monitoring and evaluating treatment response.

In terms of clinical integration, molecular receptivity tests are anticipated to become an integral component of personalized

treatment approaches, particularly in cases where pregnancy cannot be achieved despite the transfer of good-quality embryos. The wider adoption of practices such as personalized embryo transfer has the potential to increase clinical pregnancy rates. This approach replaces classical "one-size-fits-all" paradigms with treatments shaped by the biological signatures of patient-specific cycles [29].

Conclusion

Endometrial receptivity is a complex process that is at least as decisive as embryo quality in implantation success, yet it has not been adequately assessed within traditional clinical approaches. In recent years, advances in molecular biology, epigenetics, and transcriptomic analyses have enabled a more detailed characterization of the genetic and epigenetic regulators involved in this process. The expression profiles of genes such as HOXA 10, LIF, integrins, MUC1, and VEGF, together with the dynamic effects of DNA methylation, histone modifications, and non-coding RNAs, constitute the principal molecular determinants of endometrial receptivity.

In parallel with these developments, genomic-based diagnostic methods supporting personalized treatment decisions have been introduced into clinical practice. Tests such as ERA, beREADY, and Win-Test have enabled optimization of embryo transfer timing. Furthermore, the integration of artificial intelligence and bioinformatics applications has made it possible to analyze large-scale molecular datasets and to develop advanced clinical decision support systems.

The holistic perspective presented in this review encompasses not only the fundamental biology of endometrial receptivity but also current diagnostic approaches, their clinical application potential, and their technology-driven future. In this context, particularly in cases of recurrent implantation failure and unexplained infertility, individualized assessment of endometrial receptivity represents a strategic step that may significantly enhance treatment success in reproductive medicine.

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