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ENDOMETRIAL RECEPTIVITY AS A DETERMINANT OF IMPLANTATION FAILURE: FROM MORPHOLOGICAL FEATURES TO MOLECULAR MARKERS

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Abstract. Implantation failure remains one of the most challenging problems in modern reproductive medicine, particularly in the context of the widespread use of assisted reproductive technologies. In the presence of morphologically high–quality embryos, the absence of pregnancy is often associated not with embryonic factors but with endometrial dysfunction. Endometrial receptivity results from a complex

interplay of morphological, hormonal, immunological, and molecular mechanisms that ensure the formation of a temporally limited “window of implantation.” Disruption of any of these components may lead to recurrent implantation failure in both natural cycles and in vitro fertilization programs. This article summarizes current concepts regarding the morphological characteristics of the endometrium, molecular markers of receptivity, immunological factors, and their role in the development of implantation failure.

Keywords. endometrial receptivity, implantation, window of implantation, infertility, assisted reproductive technologies.

Introduction. Embryo implantation is a critical stage in the realization of female reproductive function. Despite significant advances in embryology and embryo culture technologies, the rate of clinical pregnancy in assisted reproductive technology programs remains limited. This has led to growing interest in the role of maternal factors, particularly the functional state of the endometrium. [1] The endometrium is a highly specialized tissue that undergoes cyclic changes in response to fluctuations in sex hormone levels. Only during a limited period of the menstrual cycle does it acquire the capacity to accept a blastocyst, a state defined as endometrial receptivity. [2, 3, 4] Impaired development of a receptive endometrial phenotype is considered one of the leading causes of recurrent implantation failure.

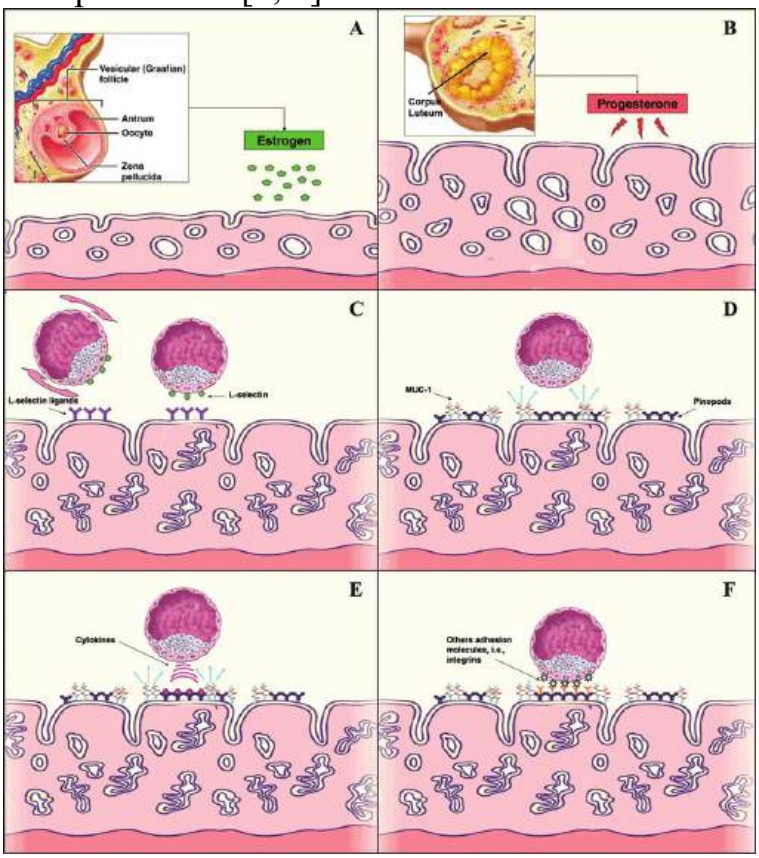
In contemporary scientific literature, the concept of endometrial receptivity has expanded beyond purely morphological assessment. The focus has shifted toward molecular, genetic, and immunological mechanisms that regulate the interaction between the endometrium and the embryo. This shift has led to the emergence of novel diagnostic approaches aimed at personalizing infertility treatment. [2, 5]

Purpose and objectives of the study. To analyze current scientific evidence on the mechanisms underlying the formation of endometrial receptivity and their role in the development of implantation failure, taking into account morphological, molecular, and immunological aspects. Objectives of the study are to characterize morphological and histological changes of the endometrium associated with receptivity; to describe the concept of the window of implantation and factors contributing to its disruption; to analyze the main molecular markers of endometrial receptivity; to evaluate the role of immunological mechanisms in the implantation process and to summarize the clinical significance of impaired endometrial receptivity in the context of infertility.

The results of the study and their discussion. The endometrium consists of functional and basal layers, each of which plays a specific role in ensuring reproductive function. The functional layer undergoes cyclic changes throughout the menstrual cycle and serves as the direct site of embryo implantation. During the proliferative phase, under the influence of estrogens, active regeneration of the endometrium occurs, accompanied by an increase in endometrial thickness and proliferation of glands and stroma. The secretory phase, which follows ovulation, is characterized by progesterone dominance and the establishment of conditions necessary for implantation. [3, 5]

A classical morphological marker of endometrial receptivity is the appearance of pinopodes–microscopic protrusions on the apical surface of the endometrial

epithelium. Although their presence was long considered a key indicator of endometrial readiness for implantation, recent studies have demonstrated limited reproducibility of this parameter. [1, 6]



(A) Endometrium proliferates under estrogen enhancement. (B) Progesterone from luteinized follicles leads to endometrial differentiation. (C) The blastocyst enters the uterus through the ostia and rolls freely over the endometrium under signals by L–selectin. (D) Mucin–1 (MUC–1) repels the blastocyst and prevents its adhesion to endometrial areas with poor chances of implantation. (E) Chemokines and cytokines attract the blastocyst to the optimal implantation spot. (F) Adhesion molecules (e.g. integrins and cadherins) firmly attach the blastocyst to the endometrial pinopods to ensure further successful implantation.

Figure 1. Human embryo implantation in the uterus.
Data generated by [7]

The window of implantation: temporal and hormonal aspects. The window of implantation is a limited period, typically between days 19 and 23 of the menstrual cycle, during which the endometrium attains maximal receptivity. [3, 5, 7, 8] Its formation depends on precise synchronization between embryonic development and hormonally driven endometrial changes. [1, 3] Even slight shifts in the timing of the implantation window may result in implantation failure. [1, 5] This is particularly relevant for patients with recurrent implantation failure in in vitro fertilization programs.

Molecular mechanisms of endometrial receptivity. Current concepts of endometrial receptivity extend far beyond morphological changes and are based on the analysis of molecular processes that regulate the interaction between the endometrium and the embryo. [4, 9] The development of a receptive phenotype is accompanied by tightly coordinated changes in gene expression, synthesis of adhesion proteins, cytokines, growth factors, and signaling molecules. [5, 7]

Adhesion molecules and cellular interaction. A key stage of implantation is the adhesion of the blastocyst to the endometrial surface. This process is mediated by cell adhesion molecules, particularly integrins. [5, 7] The most extensively studied marker of receptivity is integrin αvβ3, the expression of which increases specifically during the window of implantation. [2, 6] Reduced or absent expression of this integrin is

associated with recurrent implantation failure and endometriosis. [5] In addition to integrins, cadherins, selectins, and immunoglobulin–like molecules play an important role in ensuring stable contact between the embryo and the endometrium. Dysregulation of their expression leads to defects in attachment and subsequent trophoblast invasion. [2, 6, 7]

Cytokines and growth factors. Implantation is not merely a mechanical process but the result of complex cytokine–mediated interactions. Leukemia inhibitory factor (LIF) is considered one of the most critical cytokines required for successful implantation. [6, 10, 11] LIF deficiency is associated with infertility even in the presence of normal endometrial morphology. Other significant molecules include interleukins (IL–1, IL–15), transforming growth factor β (TGF–β), epidermal growth factor, and vascular endothelial growth factor (VEGF). [6, 10, 12] These factors regulate endometrial cell proliferation and differentiation, angiogenesis, and trophoblast invasion. [6]

Immunological aspects of implantation. Embryo implantation represents a unique immunological phenomenon, as the embryo contains paternal antigens that are potentially foreign to the maternal organism. Successful implantation is possible only when a local immune balance between tolerance and protective mechanisms is established. Uterine natural killer (uNK) cells constitute the predominant immune cell population in the endometrium during the secretory phase. [4, 11, 12] Unlike peripheral NK cells, uNK cells exhibit low cytotoxic activity and primarily perform regulatory functions. They participate in spiral artery remodeling and in the secretion of cytokines and growth factors essential for placental development. Alterations in the number or functional activity of uNK cells may lead to implantation failure, early pregnancy loss, or placental dysfunction. [1, 11, 12]

The immune response during implantation is characterized by a shift toward a Th2–type profile, which promotes immune tolerance. Predominance of a Th1–type response is associated with increased production of proinflammatory cytokines and negatively affects implantation. Regulatory T cells (Tregs) play a crucial role in maintaining immune tolerance to the embryo. [4, 11, 12, 13] A reduction in their number or function is considered a potential mechanism underlying infertility and recurrent reproductive loss.

Genomic and transcriptomic approaches to the assessment of receptivity.

Advances in molecular biology have led to the development of novel diagnostic methods aimed at evaluating endometrial receptivity at the genetic level. One of the most widely used approaches is the analysis of the endometrial transcriptomic profile. [10]

Endometrial Receptivity Analysis (ERA) is a molecular test that assesses the expression of hundreds of genes associated with endometrial receptivity. It enables identification of an individual window of implantation and personalization of embryo transfer timing. [5, 8, 10] Despite the widespread use of the ERA test, its clinical efficacy remains controversial. Some studies report improved outcomes in patients with recurrent implantation failure, whereas others demonstrate no significant difference in pregnancy rates. [8, 14] The main limitations of genomic approaches

include high cost, the invasiveness of endometrial biopsy, and the lack of universal criteria for result interpretation. [7, 10, 14] In addition, endometrial receptivity is a dynamic process that may vary between menstrual cycles. The main levels of regulation of endometrial receptivity are summarized in Table 1.

Table 1. Main levels of Endometrial Receptivity Regulation and their role in Implantation Failure

Level of regulation	Key components	Physiological role	Disorders and clinical consequences
Morphological	Endometrial thickness, glandular structure, stroma, pinopodes	Creation of a favorable environment for blastocyst adhesion	Implantation failure despite normal endometrial thickness
Hormonal	Estrogen, proge-sterone, proge-sterone receptors	Induction of secretory transformation and opening of the window of implantation	Shifted or absent window of implantation
Molecular (adhesion)	Integrins (αvβ3), cadherins, selectins	Initiation and stabilization of embryo-endometrium attachment	Impaired initial phase of implantation
Cytokine-mediated	LIF, IL–1, IL–6, TGF–β, VEGF	Regulation of trophoblast invasion and angiogenesis	Recurrent implantation failure
Immunolo-gical	Uterine NK cells, Treg cells, Th1/Th2 balance	Establishment of immune tolerance to the embryo	Immune–mediated implantation failure, early pregnancy loss
Genomic/ transcriptomic	Receptivity–associated genes (ERA profile)	Individualization of the window of implantation	Embryo transfer timing mismatch
Clinical	Hysteroscopy, endometrial biopsy	Detection of structural and inflammatory abnormalities	Underestimation of functional disorders without molecular assessment

Data generated by author

Implantation failure is a multifactorial problem involving embryonic, endometrial, and systemic factors. In clinical practice, particular attention is given to patients with recurrent implantation failure, which is generally defined as the absence of clinical pregnancy after the transfer of multiple morphologically high–quality embryos. [1, 3, 5] Endometrial factors in this patient cohort have long been underestimated. Standard assessment methods, such as ultrasonographic evaluation of endometrial thickness, do not always reflect its functional state. A normal endometrial thickness does not guarantee receptivity, as confirmed by molecular research findings. [2, 9]

Diagnostic hysteroscopy remains an important method for detecting intrauterine pathology, including synechiae, polyps, and submucosal fibroids, which may impair implantation. In addition, hysteroscopy allows the identification of indirect signs of chronic endometritis, which has a direct impact on endometrial receptivity.

Histological examination of the endometrium with immunohistochemical detection of plasma cells (CD138) is a valuable tool in the diagnosis of inflammatory changes associated with implantation failure. [4, 5, 9, 10]

Hormonal imbalance, including luteal phase insufficiency, impaired progesterone receptor sensitivity, and thyroid dysfunction, may negatively affect the development of a receptive endometrium. Metabolic disorders, chronic stress, and systemic inflammatory conditions also play a significant role. [4, 13]

Personalized approaches to the management of implantation failure. Modern reproductive medicine is increasingly shifting from standardized protocols toward personalized treatment strategies. Assessment of endometrial receptivity is a key component of this approach. Individualization of embryo transfer timing, optimization of hormonal support, and treatment of inflammatory and immunological disturbances may improve the likelihood of successful implantation. [1, 4, 9] At the same time, the lack of unified clinical guidelines regarding the use of molecular tests highlights the need for further research in this field. [2, 5]

Table 2. Evolution of Diagnostic Approaches to Endometrial Receptivity Assessment

Approach	Main method	What is assessed	Strengths	Limitations
Traditional morpholo-gical	Ultrasound, histology	Endometrial thickness, correspondence to the phase of the menstrual cycle	Widely available, non–invasive (US)	Poor prediction of implantation success
Functional hormonal	Determining the level of progesterone, luteal support protocols	Hormonal adequacy of the luteal phase	Easy to perform, clinically familiar	Doesn’t reflect tissue–level response
Inflamma-tory/ infectious	Endometrial biopsy, CD138 IHC	Chronic endometritis	Identifies treatable pathology	Invasive, cycle–dependent
Immunolo-gical	uNK cell quantification, cytokine profiling	Local immune balance	Insight into immune tolerance	Lack of standardized cut–off values
Molecular/ genomic	ERA and transcriptomic profiling	Gene expression signature of receptivity	Personalized embryo transfer timing	High cost, controversial clinical benefit
Integrated personalized approach	Multimodal assessment	Combined morphological, molecular and immune profile	Highest theoretical accuracy	Limited availability, need for validation

Data generated by author

Conclusions. Analysis of current scientific evidence indicates that endometrial receptivity is a complex, multilevel process that cannot be adequately assessed using a single marker or method. Although morphological features remain important, they

have limited prognostic value when considered without molecular and immunological aspects. The development of genomic and transcriptomic technologies has opened new opportunities for understanding the pathophysiology of implantation; however, their clinical application requires critical evaluation. Lack of standardization, high cost, and conflicting study results limit their widespread implementation. Therefore, implantation failure should be viewed not as an isolated nosological entity, but as a manifestation of imbalance between the embryo and the maternal endometrium, requiring a comprehensive and individualized approach.

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ОСОБЛИВОСТІ АТЕРОТРОМБОТИЧНИХ ЗМІН КОРОНАРНИХ АРТЕРІЙ У ПАЦІЄНТІВ З ГОСТРИМ КОРОНАРНИМ СИНДРОМОМ З ЕЛЕВАЦІЄЮ СЕГМЕНТА ST ЗАЛЕЖНО ВІД ІНДЕКСУ МАСИ ТІЛА

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Актуальність. Ожиріння є одним із ключових метаболічних чинників, що сприяє розвитку атеротромбозу та прогресуванню коронарного атеросклерозу. У пацієнтів з гострим коронарним синдромом з елевацією сегмента ST (STEMI) підвищений індекс маси тіла (ІМТ) асоціюється з більшим тромбовим навантаженням, частішим феноменом no-reflow та зростанням потреби в ургентній реваскуляризації. Вивчення ангіографічних особливостей ураження коронарних артерій залежно від ІМТ є клінічно значущим для стратифікації ризику та оптимізації тактики лікування.

Мета роботи – визначити особливості атеротромботичних змін коронарних артерій за ступенем вираженості стенозу у хворих зі STEMI залежно від індексу маси тіла.