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Is the endometrium ready for implantation? The importance of endometrial receptivity and the implantation window in RIF

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ABSTRACT

Recurrent Implantation Failure (RIF) is a multifactorial diagnosis encountered in assisted reproductive technology practice; its development is influenced not only by embryonic characteristics but also by the structural and functional status of the uterus and endometrium. This work analyzes endometrial receptivity and the "Window of Implantation" (WOI), which are critical factors for successful embryo implantation, and their potential role in RIF. It also discusses the transition of the endometrium to a receptive state under hormonal influence, the temporal synchronization between the embryo and the endometrium, and the individual nature of the WOI. Furthermore, the article examines methods for assessing the endometrium, including ultrasonography, histology, and molecular techniques, with a specific focus on endometrial receptivity tests, chronic endometritis, and the diagnostic significance of the CD138 immunohistochemical marker. Based on current scientific evidence, it is noted that endometrial receptivity and the WOI are not the sole causes of RIF and that there is insufficient evidence to support the routinal use of receptivity tests for all patients. In RIF, it is also advisable to assess endometrial factors using an individualized, complex approach that takes into account the clinical context, embryonic characteristics, and uterine status.

Keywords:

recurrent implantation failure (RIF), endometrial receptivity, window of implantation (WOI), embryo implantation, chronic endometritis, CD138

Готов ли эндометрий к имплантации? Значение рецептивности эндометрия и "окна имплантации" при Повторных Неудачах Имплантации (RIF)

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Аннотация: Повторные неудачи имплантации (RIF) – это мультифакторное состояние, с которым сталкиваются специалисты в области вспомогательных репродуктивных технологий; на его развитие влияют не только характеристики эмбриона, но и структурно-функциональное состояние матки и эндометрия. В данной работе анализируются рецептивность эндометрия и

“окно имплантации” (WOI) – ключевые факторы успешной имплантации эмбриона, - а также их возможная роль в развитии RIF. Также рассматриваются переход эндометрия в рецептивное состояние под действием гормонов, временная синхронизация между эмбрионом и эндометрием и индивидуальный характер окна имплантации. Кроме того, в статье обсуждаются методы оценки состояния эндометрия, включая ультразвуковое исследование, гистологический анализ и молекулярные методы, с особым акцентом на тесты для определения рецептивности эндометрия, хронический эндометрит и диагностическую значимость иммуногистохимического маркера CD138. На основании современных научных данных отмечается, что рецептивность эндометрия и окно имплантации не являются единственными причинами RIF, а доказательная база для рутинного применения тестов на рецептивность у всех пациенток недостаточна. При RIF также рекомендуется оценивать факторы со стороны эндометрия с использованием индивидуального комплексного подхода, учитывающего клиническую картину, характеристики эмбриона и состояние матки.

Ключевые слова: повторные неудачи имплантации (RIF), рецептивность эндометрия, окно имплантации (WOI), имплантация эмбриона, хронический эндометрит, CD138.

Endometriy implantatsiyaga tayyormi? RIF holatlarida endometrial retseptivlik va implantatsiya oynasining ahamiyati

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Annotatsiya: Takroriy implantatsiya muvaffaqiyatsizligi (RIF) yordamchi reproduktiv texnologiyalar amaliyotida uchraydigan ko’p omilli muammolardan biri bo’lib, uning rivojlanishida embrion xususiyatlari bilan bir qatorda bachadon va endometriyning strukturaviy hamda funksional holati ham muhim ahamiyatga ega. Ushbu maqolada embrion implantatsiyasining muhim shartlaridan biri bo’lgan endometrial retseptivlik, implantatsiya oynasi (Window of Implantation, WOI) va ularning RIFdagi ehtimoliy ahamiyati tahlil qilinadi. Endometriyning gormonal ta’sir ostida retseptiv holatga o’tishi, embrion va endometriy o’rtasidagi vaqt jihatdan muvofiqlik hamda WOIning individual xususiyatlari yoritiladi. Shuningdek, endometriyni ultrasonografik, gistologik va molekulyar usullar yordamida baholash imkoniyatlari, xususan, endometrial retseptivlik testlari, surunkali endometrit va CD138 immunogistokimyoviy markerining diagnostik ahamiyati ko’rib chiqiladi. Mavjud ilmiy dalillar asosida endometrial retseptivlik va WOI RIFning yagona sababi emasligi, retseptivlik testlarini esa barcha bemorlarda rutin qo’llash uchun yetarli dalillar mavjud emasligi ta’kidlanadi. RIF holatlarida endometrial omillarni baholash klinik vaziyat, embrion xususiyatlari va bachadon holatini hisobga olgan holda individual va kompleks yondashuv asosida amalga oshirilishi maqsadga muvofiq.

Kalit so’zlar: takroriy implantatsiya muvaffaqiyatsizligi (RIF), endometrial retseptivlik, implantatsiya oynasi (WOI), embrion implantatsiyasi, surunkali endometrit, CD138.

INTRODUCTION

During the IVF process, the transfer of a morphologically high-quality or viable embryo does not always guarantee successful implantation. Although it is a fact that an embryo’s developmental and implantation potential is crucial, the establishment of pregnancy depends on a complex biological interaction between the embryo and the

endometrium. Consequently, the failure of implantation to occur even after the transfer of a high-quality embryo remains a significant challenge in reproductive medicine [1]. Recurrent implantation failure (RIF) is a clinical condition characterized by the failure to achieve expected implantation or pregnancy despite repeated transfers of embryos assessed as viable during IVF. Modern approaches confirm

that defining RIF solely by the number of failed transfers is insufficient; factors such as the patient's age, embryo characteristics, outcomes of previous transfers, and individual clinical status must also be considered [2].

RIF is a multifactorial condition; its development may involve the embryo's biological characteristics, the woman's physiology, the structural and functional state of the uterus and endometrium, and treatment-related factors. Therefore, attributing RIF to a single cause is scientifically inadequate. In this context, the readiness of the endometrium to accept the embryo is an area that requires special attention [3]. The endometrium is not merely a passive environment for embryo implantation but an active biological system. Under hormonal influence during the menstrual cycle, it undergoes a series of structural and molecular changes. Consequently, within a specific time interval, the endometrium reaches an optimal functional state for embryo acceptance. This period in medicine is referred to as the "Window of Implantation" (WOI), while the readiness of the endometrium to accept the embryo and support implantation is defined as "endometrial receptivity" [4]. Temporal synchronization between embryo transfer and the endometrial receptive period is a crucial prerequisite for implantation. Theoretically, a lack of such synchronization could impact the implantation process.

However, endometrial receptivity is a multi-component biological process, and the ability to fully assess it by using a single parameter or test has not yet been conclusively proven. In particular, the clinical benefit of the routine use of commercial endometrial receptivity tests in all patients with recurrent implantation failure (RIF) has not been sufficiently established. Given this scenario, evaluating the significance of endometrial receptivity and the window of implantation in cases of RIF represents a key area of scientific and clinical inquiry.

The aim of the article is to analyze, by basing on scientific proven literature, the biological and clinical significance of endometrial receptivity and the window of implantation in cases of recurrent implantation failure (RIF), their role

in embryo implantation, and modern approaches to assessing endometrial factors.

ENDOMETRIUM AND EMBRYO IMPLANTATION

Under the influence of ovarian hormones during the menstrual cycle, the endometrium undergoes regular changes, creating a favorable environment for embryo implantation. During the proliferative phase, estrogen causes the endometrium to thicken and promotes the development of glands and stromal cells. In the post-ovulatory secretory phase, progesterone induces structural and functional changes in the endometrium in preparation for implantation. Progesterone plays a crucial role in the transition of the endometrium from a proliferative state to a receptive state. Consequently, the endometrium adapts to support embryo attachment, initial trophoblast invasion, and the implantation process. Therefore, the success of implantation depends not only on embryo quality but also on the endometrium being in a biologically receptive state at the time of transfer. For implantation to proceed effectively, the embryo's developmental stage and the endometrium's receptivity must be temporally synchronized. When the embryo arrives in the uterine cavity ready for implantation, the endometrium must also be biologically prepared to receive it. If a mismatch occurs between the embryo's developmental timing and the endometrial receptive period, the interaction between the embryo and the endometrium may be disrupted, potentially reducing the likelihood of implantation. Therefore, embryo-endometrial synchrony is considered one of the crucial conditions for successful implantation.

WHAT IS ENDOMETRIAL RECEPTIVITY?

Endometrial receptivity is the capacity of the endometrium to reach a biologically optimal state for accepting an embryo and facilitating its implantation. The brief period during which the endometrium attains this state is known as the Window of Implantation (WOI) as mentioned before. The development of endometrial receptivity is primarily regulated by the sequential action of estrogen and progesterone.

In particular, under the influence of progesterone following ovulation, molecular, cellular, and immunological changes occur within the endometrium to prepare for embryo implantation. These processes facilitate the initial interaction between the endometrium and the embryo. Thus, the timely and complete transition of the endometrium to a receptive state is a crucial period for successful embryo implantation.

“WINDOW OF IMPLANTATION” — WOI

The Window of Implantation (WOI) is the time interval during which the endometrium is sufficiently receptive to accept an embryo and support implantation. This period represents the functional state of the endometrium that is most conducive to implantation. The WOI is established through a series of endometrial changes during the menstrual cycle. Following ovulation, as the influence of progesterone increases, the endometrium transitions from a proliferative to a secretory state, and the molecular and cellular changes necessary for implantation occur. Consequently, the endometrium enters a receptive state for a specific period. For successful embryo implantation, the developmental stage of the embryo and the receptive period of the endometrium must be temporally synchronized. If the timing of the embryo transfer does not align with the endometrial receptive period, the biological interaction between the embryo and the endometrium may be insufficient, potentially reducing the likelihood of implantation. Therefore, the window of implantation (WOI) is a critical endometrial factor investigated in cases of recurrent implantation failure (RIF).

THE ROLE OF ENDOMETRIAL RECEPTIVITY IN RIF

The development of RIF is a multifactorial process in which the condition of the uterus and endometrium is just as important as embryonic characteristics. Key endometrial factors under investigation include endometrial receptivity, the characteristics of the window of implantation, endometrial thickness and morphology, chronic endometritis, and local

inflammatory processes. Other pathological changes in the uterine cavity and endometrium can also influence the implantation process. Therefore, in cases of RIF, it is crucial not to limit assessment to embryo quality alone but also to consider whether the endometrium is structurally and functionally prepared for embryo implantation. Successful implantation requires temporal synchronization between the embryo transfer and the endometrial receptive period. In some instances, an individual's endometrial receptive period may differ from the standard timeframe, potentially leading to a mismatch between the embryo transfer and the window of implantation. Consequently, individual variations in the window of implantation are being studied as a potential endometrial factor associated with RIF. However, current evidence is insufficient to classify a shift in the window of implantation as the sole or definitive cause of RIF; its clinical significance must be evaluated in conjunction with individual circumstances and other factors.

HOW CAN ENDOMETRIAL RECEPTIVITY BE ASSESSED?

Assessing endometrial receptivity involves considering the structural state, histological characteristics, and certain molecular markers of the endometrium. Since no single test can fully reflect all the functional properties of the endometrium, the assessment is conducted using a comprehensive approach tailored to the clinical situation. Transvaginal ultrasonography is a primary, non-invasive method for evaluating the endometrium. It assesses parameters such as endometrial thickness, structure, and morphology, as well as the condition of the uterine cavity and other ultrasound markers related to the endometrium. It is particularly important that the endometrium has sufficient thickness and that there are no pathological changes in the uterine cavity that could interfere with implantation. Re-evaluation of endometrial thickness is recommended in cases of recurrent implantation failure (RIF).

Histological assessment is based on the microscopic examination of a tissue sample obtained via endometrial biopsy. This method

allows for the determination of the cellular and morphological state of the endometrium, as well as the identification of certain pathological changes. Histological examination is particularly important for detecting endometrial pathologies such as chronic endometritis [5]. However, it is difficult to fully determine endometrial receptivity based solely on morphological criteria, as the implantation process involves complex molecular and cellular mechanisms. One modern approach to assessing endometrial receptivity involves molecular tests based on the analysis of gene expression within endometrial tissue. For instance, tests such as ERA (Endometrial Receptivity Analysis) are based on the concept of classifying the endometrium as receptive, pre-receptive, or post-receptive by analyzing the expression of receptivity-related genes in endometrial biopsy samples. This idea of individually tailoring the timing of embryo transfer based on such tests has been proposed [6]. However, current evidence has not sufficiently confirmed the clinical benefit of the routine use of these tests in all patients with RIF. Chronic endometritis is a condition characterized by persistent inflammation of the endometrium, which can negatively affect the implantation process in some patients. Endometrial biopsy and histological examination are used for its diagnosis [7]. A key feature of chronic endometritis is the presence of plasma cells in the endometrial stroma. The CD138 marker is used in immunohistochemical analysis to facilitate the detection of these cells [8]. Therefore, CD138 is not a test that specifically identifies RIF; rather, it is an immunohistochemical marker that aids in the diagnosis of chronic endometritis by detecting plasma cells in an endometrial biopsy [9].

IS ASSESSMENT OF ENDOMETRIAL RECEPTIVITY NECESSARY FOR EVERY RIF PATIENT?

While evaluating endometrial factors is important in cases of RIF (Recurrent Implantation Failure), it is not necessary to automatically perform the same set of tests on all patients. Since RIF is a multifactorial condition, diagnostic procedures should be

individualized based on the patient's medical history, previous IVF cycles, embryo characteristics, and the condition of the uterus and endometrium. Molecular tests, such as ERA, aim to assess endometrial receptivity and the individual characteristics of the implantation window. However, current evidence does not sufficiently support the clinical benefit of routinely using these tests for all RIF-patients; therefore, their use as a standard diagnostic procedure is not recommended.

Endometrial biopsy is not considered a mandatory test for all RIF-patients solely to determine receptivity. However, in certain clinical situations particularly when endometrial pathology is suspected, a biopsy can be useful for histological assessment and the detection of chronic endometritis. Testing for chronic endometritis may be considered in specific RIF cases, utilizing histological examination of the endometrial biopsy and CD138 immunohistochemical staining. At the same time, evidence in this area is limited due to the lack of a unified standard for diagnosing chronic endometritis, specifically regarding the threshold for plasma cell counts [10]. Testing is selected based on the clinical situation, primarily for patients who have experienced recurrent implantation failure (RIF), those with suspected endometrial or uterine pathology in previous IVF cycles, or those at risk for conditions such as chronic endometritis. Re-evaluation of the uterine cavity via ultrasound, sonohysterography, or hysteroscopy is also a crucial component of the RIF workup. Thus, a clinically justified, stepwise diagnostic approach, rather than the sequential performance of every available endometrial test, is considered the scientifically sound strategy for patients with RIF. Although receptivity tests and the assessment of the WOI may hold potential value in certain cases, their clinical utility has not yet been fully established.

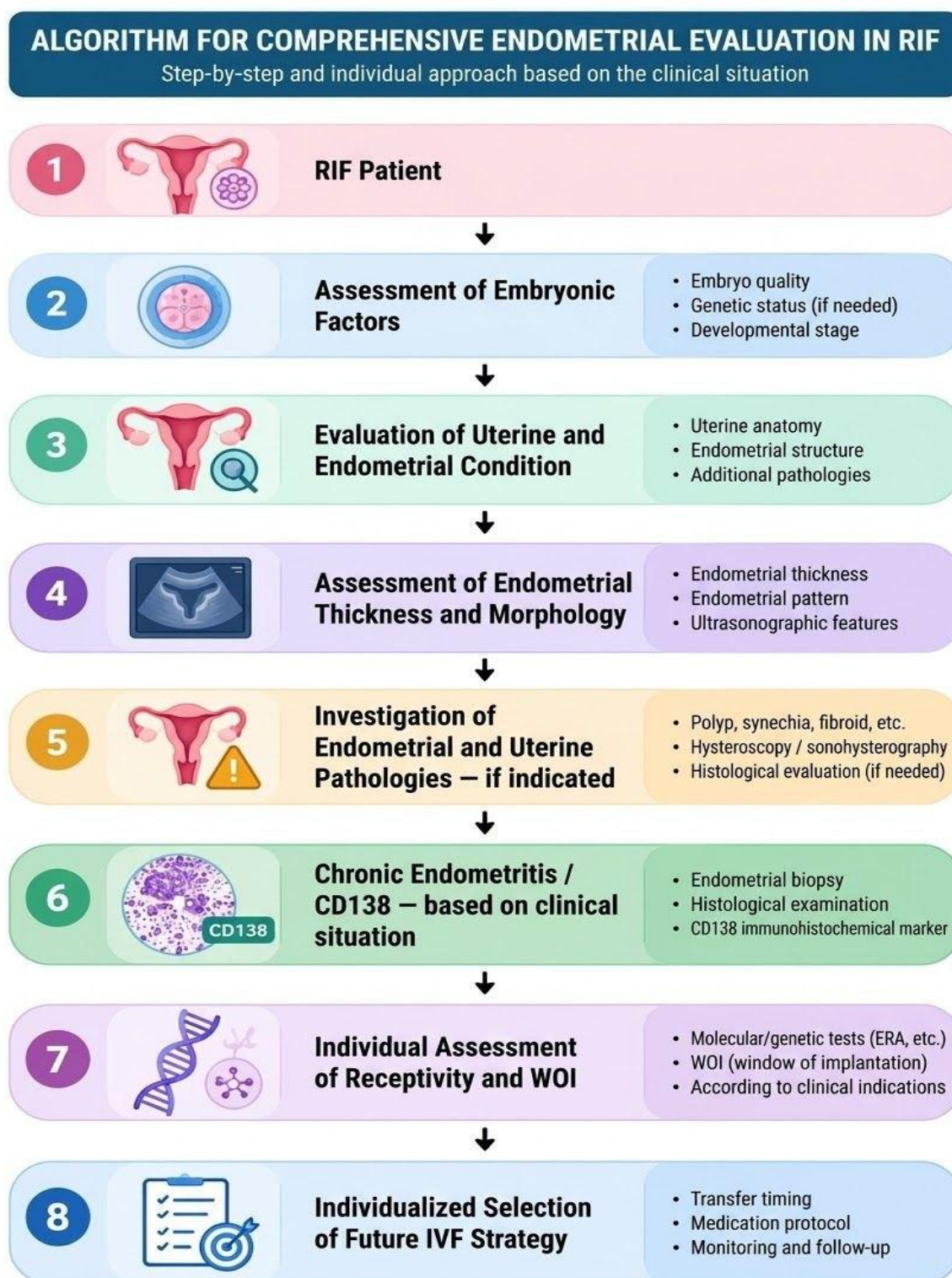
A COMPLEX APPROACH TO ENDOMETRIAL ASSESSMENT IN RIF

Since RIF is a multifactorial condition, endometrial assessment should not rely on a single test. The clinical approach involves a stepwise evaluation of embryonic factors, the

structural status of the uterus and endometrium, and, where necessary, endometrial pathologies. In this approach, the objective of each examination must be clearly defined. Initially, factors related to the embryo and the baseline status of the uterus and endometrium are assessed. Subsequent examinations are selected based on identified clinical issues or the specific characteristics of the RIF case. Endometrial assessment in RIF

relies not on a “one-size-fits-all” testing strategy, but rather on an individualized, stepwise, and clinically justified approach.

Figure 1 demonstrates stages for comprehensive endometrial assessment in RIF. During our research, in order to show the steps, we ourselves created the procedure picture to clearly outline all the mentioned data provided above.



In RIF, endometrial assessment is performed in a stepwise manner. Examinations are individualized based on the clinical situation, and the subsequent IVF strategy is determined according to the identified issues.

DISCUSSION

It is incorrect to attribute RIF solely to impaired endometrial receptivity. The outcome of implantation is determined by the interplay of factors including the embryo's biological characteristics, uterine anatomy, the structural and functional state of the endometrium, and aspects of the reproductive treatment itself.

Therefore, endometrial factors must be evaluated alongside other potential causes of RIF. As we know, implantation relies on a complex biological interaction between the embryo and the endometrium. Even if the embryo possesses implantation potential, implantation may fail if the endometrium lacks the appropriate functional state. Conversely, an optimal endometrial environment cannot overcome issues related to the embryo's developmental or genetic characteristics. Thus, in cases of RIF, embryonic and endometrial factors must be considered in conjunction. Individual characteristics of the WOI are being investigated as a crucial aspect of the implantation process. Theoretically, a mismatch between the timing of embryo transfer and the endometrial window of receptivity could affect implantation.

However, the clinical significance of a WOI shift in RIF remains undetermined, and there is insufficient evidence to classify it as an independent cause of RIF. Molecular tests, such as the ERA, offer the possibility of personalizing the timing of embryo transfer based on endometrial gene expression. Although initial studies demonstrated the potential benefit of this approach, subsequent research, including a randomized clinical trial, did not confirm that adjusting the time of transfer based on ERA significantly improved live birth rates [11]. Consequently, current evidence does not support the routine use of these tests in all patients with RIF. Chronic endometritis is another endometrial factor potentially associated with RIF. Its diagnosis involves endometrial biopsy, histological assessment, and CD138 immunohistochemical staining.

On other hands, the absence of a uniform diagnostic threshold for plasma cells and fully standardized criteria complicates the comparison of study results. Therefore, CD138 results should be interpreted in conjunction with clinical data and other diagnostic findings. Overall, given the clinical heterogeneity of RIF patients, it is inappropriate to directly extrapolate endometrial changes or test results identified in one patient to the entire RIF patient population. Current evidence underscores the need to select diagnostic tests tailored to the

specific clinical situation, avoid the routine use of tests lacking proven clinical benefit, and comprehensively evaluate embryonic, uterine, and endometrial factors.

CONCLUSION

Recurrent Implantation Failure (RIF) is a multifactorial reproductive issue involving the interplay of embryonic, uterine, and endometrial factors. The structural and functional status of the endometrium, specifically endometrial receptivity and the window of implantation, determines the critical biological conditions for embryo implantation. In RIF, endometrial factors should be assessed based on the clinical context, with investigations for endometrial pathologies and chronic endometritis conducted when necessary. At the same time, the clinical utility of receptivity tests, assessment of the window of implantation (WOI), and other additional examinations must be evaluated on an individual basis, grounded in available evidence. Therefore, a comprehensive and personalized approach that simultaneously considers embryonic, uterine, and endometrial factors is essential in the management of patients with RIF.

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