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MORPHOLOGICAL AND MOLECULAR BIOLOGICAL DETERMINANTS OF REPEATED IMPLANTATION FAILURE

Abstract. The evolution of assisted reproductive technology (ART) from classical in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) to the era of predictive models using artificial intelligence has led to a worldwide reproductive revolution in recent years. But despite the significant development of ART, there is still a high prevalence of failed IVF attempts. Thus, although ART improves overall outcomes for infertile couples, some problems still remain unresolved, such as repeated implantation failure (RIF). The term RIF is applicable only in IVF programs. RIF is a complex and urgent problem of modern reproductology. It has a wide range of understudied etiological factors and pathogenesis mechanisms. The pathogenesis of implantation failures is based on a variety of polygenic and polymorphic mechanisms of defective receptivity due to disturbance of endometrial architectonics. Management of RIF should be individualized taking into account its pathogenesis patterns using methods based on the principles of evidence-based medicine. Randomized clinical trials with large statistical samples and with a thorough consideration of clinical and morphological patterns are necessary to understand the mechanisms of its realization further and to overcome the problem.

Key words: in vitro fertilization, repeated implantation failure, assisted reproductive technology.

The evolution of ART from classical IVF and intracytoplasmic sperm injection (ICSI) to the era of predictive models using artificial intelligence has led to a worldwide reproductive revolution in recent years. The etiology of infertility is considered multifactorial, and some of its key aspects include genetic abnormalities of male and female origin, ovulation disorders, tubal obstruction, uterine or peritoneal disorders associated with female infertility, as well as male factors, such as poor sperm quality [2]. In 2019, the European Society for Human Reproduction and Embryology (ESHRE) published a press release based on statistical analysis of a large data set. According to them, 20–30% of infertility is associated with male factors, 20–35% is associated with female etiology, and 25–40% is a combination of female and male infertility factors. The remaining 10–20% are classified as idiopathic infertility, and most of these couples suffer from repeated implantation failure (RIF) [3].

Thus, despite the significant development of ART, there is still a high prevalence of failed IVF attempts. There are many studies and reviews focused on various factors, from uterine anatomy and endometrial receptivity to connective tissue disorders and immunological factors that negatively or

positively affect IVF success rates. Although ART improves overall outcomes for infertile couples, some problems still remain unresolved, such as RIF.

The term RIF is applicable only in IVF programs. Although there is no generally accepted formal definition of repeated failure of implantation, Orvieto et al (2015) offer a definition that implies three unsuccessful in vitro fertilization cycles with good quality embryo transfer [4]. Researchers at Zeyneloglu et al (2014) agree that this clinical situation can be established after three failed IVF cycles, especially when transferring two high-quality embryos [5]. The data of Simon, Laufer et al (2012) add to the definition that anatomical disorders of the embryo and a decrease in the receptivity of the endometrium can play a key role in the development of RIF [6]. To define RIF, it is also important to take into account the age of the mother and determine whether the embryos were transferred at the stage of fragmentation or blastocyst [7]. Coughlan et al (2014) offer a more complete working definition based on maternal age, number of embryos transferred, and number of completed cycles. They define RIF as non-occurrence of clinical pregnancy after 4 transfers of "fresh" or thawed good embryos in women under 40 years of age [8]. In the clinical protocol of the Ministry of Health of the Russian Federation in 2019, such a clinical situation is called "Repeated unsuccessful attempts at transferring embryos (implantation)" and refers to it as cases of 3 unsuccessful attempts at elective (eSET or eDET) transfer of "fresh" or thawed embryos in women under 35 years of age, and 2 - in women 35 years of age and older, in the absence of any factors that reduce the chances of pregnancy [9].

Failure to implant embryos may be due to female, male, or fetal factors, or a specific type of IVF protocol. Each clinical situation should be carefully studied to determine the most likely etiology of the disease, since RIF is a complex problem with several variables. There are many risk factors for RIF, including maternal age, smoking of both parents, increased body mass index and stress level [10,11,12,13,14]. Immunological factors, such as the level of cytokines and the presence of specific autoantibodies, as well as any infectious pathogens leading to chronic endometritis, should be investigated in each individual patient with RIF. Uterine neoplasms, such as polyps and fibroids, and congenital anatomical abnormalities should also be excluded. Sperm analysis, preimplantation genetic screening and endometrial receptivity should be reviewed and evaluated.RIF in order to propose new solutions and develop individual approaches for specific patients or groups of patients.

Pathogenetic mechanisms of implantation failures. Endometrial receptivity. You cannot talk about implantation without considering such an important aspect of a woman's reproductive system as endometrokh. Sxz;.jika ewlp[w;pm [vmckdo8ial receptivity. Implantation is a complex process resulting from the correct interaction between the endometrium and the blastocyst. According to various estimates, only 30% of all implantation failures account for embryonic abnormalities, while the suboptimal susceptibility of the endometrium and the altered dialogue between embryos and endometrium are responsible for the remaining two-thirds [15]. Endometrial susceptibility has been the subject of extensive debate for over 80 years since Rock and Bartlett et al described histological changes in the endometrium in the implantation window in 1937 [16]. From that moment, a tremendous path has been made in the study of endometrium, and flow cytometry and advances in molecular biology have allowed further studies of the cross-linking between the embryo and endometrium [17]. Omics also greatly helps in the study of receptivity and implantation. It is the field of research with highly sensitive methods that allow simultaneous study of changes at various molecular levels: genomics, transcriptomics, proteomics, metabolomics, etc. Understanding the physiology and pathophysiology of the human endometrium is being revolutionized through the use of omics [18].

Although recent advances have led to a deep understanding of the processes associated with the cross-dialogue between the embryo and the endometrium during implantation, the cause of their impairment remains a mystery, and significant progress in transforming the findings into clinically relevant prognostic tests and treatments for suboptimal susceptibility of the endometrium has not been achieved.

The susceptibility and selectivity of the endometrium are two complementary concepts introduced to describe the endometrium as a biosensor that evaluates the quality of the embryo [19]. Selectivity is a built-in programmed function of the endometrium for recognition and rejection of embryos with reduced development potential. On the contrary, susceptibility allows the endometrium to provide an optimal environment for embryo development and placenta formation.

An extensive meta-analysis of 2019, which included 163 studies (88834 women) [20], allowed to identify the main markers of endometrial receptivity:

– Ultrasound markers evaluated on the day the ovulation trigger is administered and on the day of embryo transfer:

- Endometrial thickness;
- Three-line structure;
- Endometrial volume;
- Pulsation index of the uterine arteries;
- Resistance indicators in the uterine, arcuate, radial, basal and spiral arteries;
- Uterine contractions on the day of embryo transfer;

– Markers in endometrial biopsy:

- BLC6;
- α-Inhibin;
- β-Glycan;
- luminal integrin αvβ3;
- L-selectin ligand;
- Aromattase P450;
- vascular endothelial growth factor A;
- expression of matrix metalloproteinases and E-cadherin;
- alpha-2 PEG;
- hCG-LH receptor;
- LIF (leukemia inhibitory factor);
- colony-stimulating macrophage factor;
- HOXA-10;
- Counting pinopods by electron microscopy (at least 60 fields at × 2000 magnification);
- ERA;

– Markers in endometrial fluid aspirate:

- Concentration of hDP 200 (Human decidua-associated protein 200);
- LIF (leukemia inhibitory factor);
- TNF-α;
- IL-18;

– Hysteroscopic assessment:

- ring type of arrangement of glands and the presence of well-developed varicose vessels;
- Endometrial blood flow >29 mL/min/100 g.

While some studies in this 2019 meta-analysis showed high sensitivity in assessing endometrial receptivity by certain markers, others showed opposite data. Therefore, it is impossible to draw conclusions regarding the clinical use of certain markers in the practice of a reproductologist, although many authors distinguish ultrasound criteria, as well as the ERA test, as the most effective [21,22,23]. The main factor limiting the quality of evidence supporting the sensitivity of endometrial receptivity markers, measured by biopsy, fluid aspirate, ultrasound, or hysteroscopy, was inaccuracy in the studies. Most markers have so far been studied only in small samples, and that leads to uncertainties regarding its reproducibility, their true effect, and clinical value.

Immunological mechanisms. In the recent years great importance has been given to the immunological mechanisms of the formation of endometrial insufficiency in the study of the etiopathogenesis of repeated implantation failures, especially in the absence of a macroscopic substrate or signs of chronic endometritis.

Uterine NK cells, Uterine Natural Killer (uNK) are primarily responsible for the implementation of the immune response in the uterine cavity. They come from the NK cell line and differ in the marker CD56 +, however, they do not have the same ability to destroy cancer cells and other foreign HLA class 1 molecules, therefore, they do not have a harmful effect on the implanted embryo. Due to the similar phenotype, CD117 + CD94-CD3-, it is likely that peripheral NK cells at the 3 stages of their development migrate to the endometrium and complete their maturation and development already there, subsequently becoming uNK cells [24]. In fact, they are the dominant type of immune cells in the uterine mucosa, and it has been suggested that they play a role in trophoblast invasion and increased blood flow through the

spiral arteries. Measuring the level of uNK cells seems difficult, as it fluctuates during the menstrual cycle due to changes in the level of progesterone and other hormones. As a result, any change in hormonal levels in healthy fertile women can affect the level of uNK cells without any effect on the outcome of pregnancy.

During implantation, uNK through paracrine signals stimulate endometrial epithelial cells to produce IL-15, VEGF, and other factors that can regulate the proliferation of uNK cells. An immune paracrine connection between uNK and endometrial epithelial cells promotes implantation and development of trophoblast [25].

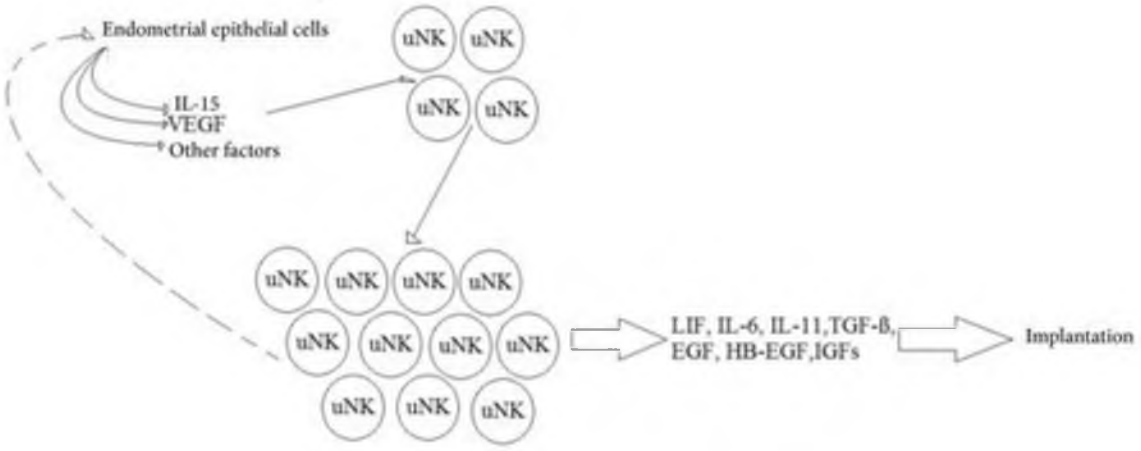

Figure 1 – Schematic representation of the role of uNK in implantation

A study published by Santillan et al (2015) showed that both peripheral NK cells and uNK levels are elevated in patients with failed implantation. Blood NK cell levels were 13.4 ± 1.2% (range 2.63–29.01) in patients with repeated failure of implantation and 8.4 ± 0.7% (range 5.72–13.28) in the control group. UNK levels were measured using an endometrial biopsy, and levels exceeding 250 CD56 + cells in a 400× high power field were detected in 53% of patients with idiopathic implantation failures and only 5% in the control group. These measurements became possible by imaging uterine NK cells with immunohistochemical staining. Although thresholds still require standardization, NK cell analysis may ultimately prove useful for women suffering from idiopathic repeated implant failure [26]. On the other hand, a meta-analysis by Seshadri et al (2014), aimed at determining the role of NK cells in both peripheral blood and the uterus in infertility, revealed some conflicting data on their role. There were no significant differences in peripheral (SMD -0.33; 95% CI -1.06; 0.40; P = 0.37) and uterine (SMD -1.82; 95% CI-4.80; 1, 17; P = 0.23) NK cell levels, expressed as percentages, although in studies in which they were expressed as numerical values, there were significantly higher levels of peripheral NK cells in infertile women (SMD 3.16; 95% CI 1.07; 5.24; P = 0.003). In addition, NK cell levels are apparently not related to the birth rate in people undergoing IVF programs (RR 0.57; 95% CI 0.06; 5.22; P = 0.62). This study also recorded significantly higher percentages of peripheral NK cells (SMD 1.36; 95% CI 0.04; 2.69; P = 0.04) and numbers (SMD 0.81; 95% CI 0 , 47; 1.16; P <0.00001), but there were no significant differences in uNK cell levels between women with repeated implantation failures and the control group (SMD 0.40; 95% CI -1.24; 2.04 ; P = 0,063). It remains unclear why measurements of NK cells in absolute and relative indices give different results [27].

Sacks et al. found that the concentration of peripheral NK cells (0.23 × 109/L ± 0.11 vs. 0.20 × 109/L ± 0.13) and their percentage (> 18%, threshold) in lymphocytes were significantly increased in women with failed implantation compared to the control group. Nevertheless, it is important to note that the sensitivity of this test was only 11%, which suggests that in patients with failed implantation many other factors can play a role and contribute to difficulties in achieving pregnancy. According to the authors of the study, determining the level of NK cells cannot be used as a predictor of implantation failures in the general population, but it can be used in women with an already established diagnosis to determine whether etiology is related to their immunological profile [28].

In a 2019 meta-analysis studying a cohort of infertile women [29], it was concluded that there is no difference in NK concentrations of peripheral blood if the phase of the menstrual cycle was ignored in the measurement. However, in the secretory phase, the authors observed a higher proportion of circulating NK cells in women suffering from infertility.

The authors also studied the relationship between the concentration in the peripheral blood of large T-cell granular lymphocytes (post-thymic antigen-primed, constitutively activated CD3 + CD8 + T-lymphocytes characterized by the presence of cytotoxic granulations in the cytoplasm and co-expression of CD57 (CD3 + CD8 + CD57 +) and repeated implantation failures. Based on their data, it can be concluded that the levels of CD3-CD56 + and CD8 + CD57 + cells in peripheral blood are not associated with repeated implantation failures and cannot be recommended as markers [29].

The role of NK cells in implantation failure remains in the process of study and causes many contraverses. The level and activity of NK cells is just one aspect of the immune system in women suffering from infertility, and more data are needed to analyze them clinically.

The role of microRNA. Promising data have been published regarding intracellular genetic mechanisms for the mechanisms of endometrial insufficiency and implantation failure. MicroRNAs (miRNAs) play a key role in regulating gene expression by inhibiting translation and controlling post-transcriptional modifications. There are studies showing that miRNAs provide pathways involved in the regulatory mechanisms of human reproduction, including the formation and maintenance of primordial follicles, spermatogenesis, oocyte maturation, folliculogenesis, and corpus luteum function [31,32,33,34]. Previously, a connection was found between miRNA expression and infertility, polycystic ovary syndrome, premature ovarian failure, and repeated failure of implantation [35,36].

Thirteen different miRNAs have already been identified in endometrial samples of patients, with repeated implantation failures that presumably regulate the expression of 3800 genes and which were not found in the group of healthy women. It was also shown that ten miRNAs are overexpressed in endometrial samples in women with repeated implantation failures, including miR-23b, miR -199a, and miR-145 [37].

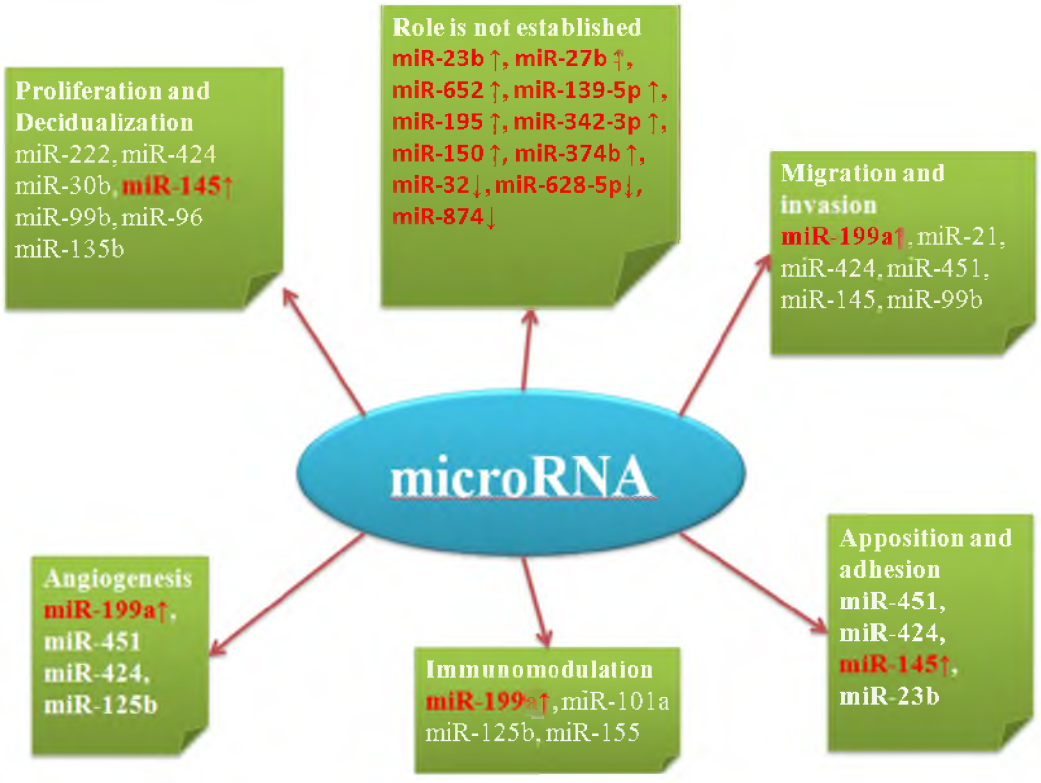

Figure 2 – The established role of miRNAs in implantation and impaired expression in RIF

The role of biocenosis. An important and understudied aspect of endometrial viability is the state of the vaginal and endometrial biocenosis. A study conducted in 2019 compared the microbiological composition of endometrial aspirate and vaginal discharge in women with RIF and a control group. Data of this study showed that the Shannon index (biodiversity index) of vaginal discharge was statistically significantly lower in the RIF group compared with the control group (p = 0.02), while a comparison of the same index in endometrial aspirates did not reveal differences [24].

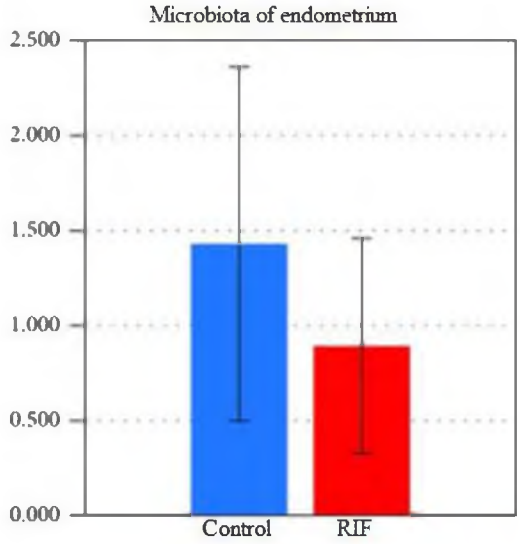

Figure 3 – Comparison of the Shannon index of the biocenosis of endometrial aspirate [38]

The unweighted Unifrac distance (an indicator used to compare biological communities) of the microbiota of the endometrial aspirate showed a significant difference between the RIF group and the control group (p = 0.0089). Meanwhile, the same indicator of vaginal discharge was the same in both groups (p = 0.38). The microbiota of endometrial aspirate with a predominance of lactobacilli, determined by the status of the genus Lactobacillus> 90%, was observed with a higher frequency in the RIF group (64.3%) rather than in the control group (38.9%) (p = 0.13). Similar results were obtained for the vaginal microbiota: 67.9% in the RIF group and 44.4% in the control group was the microbiota with a predominance of lactobacilli (p = 0.14). The detection rate of Gardnerella in the EF microbiota was 39.3% in the RIF group and 27.7% in the control group (p = 0.53). Burkholderia was not detected in any of the microbiota of the endometrial aspirate in the control group, but was found in 25% of the RIF group (p = 0.032). Some studies have shown that Burkholderia are often detected in the uterine cavity in patients using the intrauterine device contraceptive system with levonorgestrel [39], in another study, the authors suggest that Burkholderia may be one of the potential pathogens that cause tubovarian abscess [40]. The effect of Burkholderia on endometrial susceptibility requires further studying. There were no significant differences in the frequency of detection of certain types of bacteria in the microbiota of the vaginal discharges between the two groups.

Genetic Disorders. A 2019 study [41] examined the hypothesis that transcriptome analysis of follicular cells after failed IVF cycles can reveal potential causes of implantation failures and provide new information about their pathophysiological mechanisms. Real-time PCR showed 165 differentially expressed genes in the group of patients with implantation failures compared with the group of pregnant women. These genes included many pro-inflammatory cytokines and other factors associated with inflammation. Overexpression of several factors, some of which regulate the activity of vascular endothelial growth factor, also indicates increased permeability and vasodilatation in the pathogenesis of RIF. Some genes have been associated with abnormal differentiation and increased apoptosis [41]. Thus, it can be assumed that failure of implantation in IVF cycles may be associated with an imbalance between pro-inflammatory and anti-inflammatory mediators.

Promising data were obtained in a study by Diaz-Nuñez et al. in 2019 regarding coagulation factors and their association with RIF. In this prospective study, women with repeated implantation failures were

subjected to a ThromboinCode analysis to identify 12 genetic variants of factors V Leiden, V Hong Kong, V Cambridge, II, XIII, XII and A1. Higher values were observed in the RIF group (70%) compared with the control group (52.94%) and the population of Spain in general (56.5%) regarding XII coagulation factor (p = 0.043) [42].

Conclusion. Repeated implantation failure is a complex and urgent problem of modern reproductology, which has a wide range of understudied etiological factors and pathogenesis mechanisms. Based on the analysis of modern literature, it can be concluded that there is still no consensus regarding the definition of repeated implantation failure, reliable risk factors and implementation mechanisms, as well as methods for overcoming them. The main reason for the failure of implantation is a disturbance of the receptivity of the endometrium [43]. And the basis of the pathogenesis for each individual patient differs due to etiological factors and mechanisms, which include changes in the architectonics of the endometrium, impaired immune status, neoangiogenesis, vasodilatation, defects of coagulation factors, genetic factors and even microbiota imbalance. Management of RIF should be individualized taking into account its pathogenesis patterns using methods based on the principles of evidence-based medicine. Taking into account clinical and morphological patterns randomized clinical trials on large statistical samples are necessary to study the mechanisms of its realization further and overcoming the problem.

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ҚАЙТАЛАНГАН ИМПЛАНТАЦИЯ СӘТСІЗДІГІНІҢ МОРФОЛОГИЯЛЫҚ ЖӘНЕ МОЛЕКУЛЯРЛЫ-БИОЛОГИЯЛЫҚ ДЕТЕРМИНАНТТАРЫ

Аннотация. Қосалқы репродуктивті технологиялардың (ҚРТ) классикалық Экстрокорпоралды ұрықтанудан (ЭКҰ) және сперматозоидтарды интрацитоплазмалық инъекция жасаудан (ICSI) жасанды интеллектті қолдана отырып болжанатын модельдер дәуіріне дейінгі эволюциясы соңғы жылдары дүниежүзілік репродуктивті революцияға ықпал етті. Бірақ ҚРТ-ның айтарлықтай дамуына қарамастан, сәтсіз Экстрокорпоралды Ұрықтандыру әрекеттерінің жоғары таралуы сақталады. Осылайша, ҚРТ бедеулік жұптардың жалпы нәтижелерін жақсартса да, кейбір проблемалар әлі де шешілмеген, мысалы, имплантацияның қайталама сәтсіздігі (ИҚС). Имплантацияның қайталама сәтсіздігі терминӊ тек ЭКҰ багдарламалары бар паңиенттерге қолданылады. ИҚС – бұл аз зерттелген этиологиялық факторлар мен патогенетикалық механизмдердің кең спектріне ие қазіргі замангы көбеюдің күрделі және өзекті мәселесі. Имплантация сәтсіздігінің патогенезі эндометриялық архитектониканың, иммундық мәртебенің, неоангиогенездің, вазодиляцияның, коагуляция факторларының, генетикалық факторлардың және тіпті биоңеноздың бұзылуының аясында ақаулы реңептивтіліктің әртүрлі полигендік және полиморфты механизмдеріне негізделген. Соңғы жылдары имплантацияның қайталама сәтсздік ақауларының этиопатогенезін зерттеуде, әсіресе, макроскопиялық субстрат немесе созылмалы эндометрит белгілері болмаган кезде, эндометриялық дәрменсіздіктің пайда болуының иммунологиялық механизмдеріне көбірек мән беріліп келеді. Соңғы жылдардағы жетістіктер имплантация кезінде эмбрион мен эндометрий арасындагы айқас диалогпен байланысты проңестерді терең түсінуге әкелсе де, олардың бұзылуының себебі құпия болып қала береді, ал нәтижелерді эндометрияның субоптималды сезімталдығын емдеуге арналган клиникалық маңызды болжамдық сынақтар мен емдеулерге айналдыруда айтарлықтай жетістіктерге қол жеткізілген жоқ. ИҚС-нің көптеген маркерлері кішкентай үлгілерде гана зерттелген, бұл, олардың репродуктивті жағдайга қатысты белгісіздікке, шынайы әсеріне және клиникалық құндылығына қатысты белгісіздікке әкеледі. ҚИС-гі бар бедеулік жұптардың емдеу тактикасын дәлелді медиңина қағидаттарына негізделген әдістерді қолдана отырып, патогенетикалық заңдылықтарды ескере отырып жекелеу керек. Мәселенӊ енгізу және шешу тетіктерін одан әрі зерттеу үшін клиникалық және морфологиялық ерекшеліктерді ескере отырып, ірі статистикалық үлгілерде рандомизацияланган клиникалық зерттеулер қажет.

Түйін сөздер: Экстрокорпоралды ұрықтандыру, имплантацияның қайталама сәтсіздігі, қосалқы репродуктивті технологиялар.

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МОРФОЛОГИЧЕСКИЕ И МОЛЕКУЛЯРНО-БИОЛОГИЧЕСКИЕ ДЕТЕРМИНАНТЫ ПОВТОРНЫХ НЕУДАЧ ИМПЛАНТАЦИИ

Аннотация. Эволюция вспомогательных репродуктивных технологий (ВРТ) от классического экстракорпорального оплодотворения (ЭКО) и интрацитоплазматической инъекции сперматозоидов (ИКСИ) к эпохе моделей прогнозирования, использующих искусственный интеллект, в последние годы способствовала всемирной репродуктивной революции. Но, несмотря на значительное развитие ВРТ, по-прежнему присутствует высокая распространенность неудачных попыток ЭКО. Таким образом, хотя ВРТ и улучшает общие результаты для бесплодных пар, некоторые проблемы до сих пор остаются нерешенными, например, повторные неудачи имплантации (ПНИ). Термин повторные неудачи имплантации применим только к пациентам в программах ЭКО. ПНИ – это сложная и актуальная проблема современной репродуктологии, имеющей широкий спектр малоизученных этиологических факторов и патогенетических механизмов. В основе патогенеза неудач имплантации лежат разнообразные полигенные и полиморфные механизмы дефектной рецептивности на фоне нарушений архитектоники эндометрия, иммунного статуса, неоангиогенеза, вазодилатации, дефектов факторов свертывания, генетических факторов и даже нарушений биоценоза. Последние годы в изучении этиопатогенеза повторных неудач имплантации всё большее значение уделяется иммунологическим механизмам формирования несостоятельности эндометрия, особенно в отсутствии макроспического субстрата или признаков хронического эндометрита. Хотя достижения последних лет привели к глубокому пониманию процессов, связанных с перекрестным диалогом эмбриона и эндометрия во время имплантации, причина их нарушений остается загадкой, и значительный прогресс в преобразовании открытий в клинически значимые прогностические тесты и методы лечения субоптимальной восприимчивости эндометрии достигнут не был. Большинство маркеров ПНИ пока что изучались лишь на маленьких выборках, что приводит к неопределенности в отношении воспроизводимости, истинного их эффекта и клинической ценности. Тактика ведения бесплодных пар, страдающих ПНИ, должна быть индивидуализирована с учетом патогенетических паттернов с применением методов, основанных на принципах доказательной медицины. Для дальнейшего изучения механизмов реализации и преодоления проблемы необходимы рандомизированные клинические испытания на больших статистических выборках с учетом клинико-морфологических особенностей.

Ключевые слова: экстракорпоральное оплодотворение, повторные неудачи имплантации, вспомогательные репродуктивные технологии.

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