



THIN ENDOMETRIUM AND IMPLANTATION FAILURE IN ART/IVF: DIAGNOSTIC CRITERIA, ENDOMETRIAL RECEPTIVITY MARKERS, AND CONTEMPORARY TREATMENT STRATEGIES

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Abstract.

Background. Uterine-factor infertility, including thin endometrium and impaired endometrial receptivity, remains a major contributor to repeated implantation failure in ART/IVF. The absence of a universally accepted thickness threshold and the lack of a broadly accurate, accessible receptivity test complicate clinical decision-making.

Objective. To summarize diagnostic criteria for thin endometrium, review ultrasound and molecular markers of receptivity, and appraise evidence for conventional and emerging therapeutic options in women with reproductive failure.

Materials and Methods. A narrative review of Russian and international literature addressing endometrial thickness and pattern (M-echo, trilaminar morphology and classification), uterine/subendometrial perfusion, chronic endometritis, molecular markers (LIF, VEGF, integrins, pinopodes), and treatment strategies (estrogen supplementation, vasoactive agents, physical modalities, endometrial injury/scratching, intrauterine G-CSF, PRP, and cell-based therapies).

Results. Most studies report reduced pregnancy rates when endometrial thickness is <7 mm; however, successful implantation and live birth have been documented at lower thickness values when morphology and receptivity are favorable. Key etiologic factors include repeated intrauterine procedures, chronic inflammation, vascular/hemodynamic impairment, and hormonal disturbances. Regenerative and angiogenesis-oriented approaches (PRP, G-CSF) appear promising, while evidence for ERA-guided personalized transfer remains controversial.

Conclusion. Thin endometrium is a multifactorial condition requiring integrated assessment (morphology, inflammation, perfusion, and receptivity markers) and individualized management. High-quality RCTs using harmonized definitions and clinically meaningful endpoints (live birth) are needed to establish optimal care pathways.

Key words: thin endometrium; endometrial receptivity; window of implantation; recurrent implantation failure; in vitro fertilization; uterine artery Doppler; platelet-rich plasma.

ТОНКИЙ ЭНДОМЕТРИЙ И ИМПЛАНТАЦИОННЫЕ НЕУДАЧИ В ПРОГРАММАХ ВРТ: ДИАГНОСТИЧЕСКИЕ КРИТЕРИИ, МАРКЕРЫ РЕЦЕПТИВНОСТИ И СОВРЕМЕННЫЕ ПОДХОДЫ К ТЕРАПИИ

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Аннотация.

Актуальность. Утеринный фактор бесплодия, включая гипоплазию («тонкий») эндометрия и нарушение его рецептивности, остается одной из ключевых причин повторных имплантационных неудач в программах ЭКО. Отсутствие универсального порога «тонкого» эндометрия и ограниченная доступность точных тестов «окна имплантации» затрудняют клинические решения и стандартизацию тактики ведения.

Цель исследования. Систематизировать данные о диагностике «тонкого» эндометрия,

ультразвуковых и молекулярных маркерах рецептивности, а также оценить доказательную базу традиционных и инновационных методов лечения у пациенток с репродуктивными неудачами.

Материал и методы. Проведен обзор отечественных и зарубежных публикаций по оценке толщины и структуры эндометрия (М-эхо, трилинейный паттерн, классификации), гемодинамике маточных сосудов, хроническому эндометриту, молекулярным маркерам (LIF, VEGF, интегрины, пиноподии), а также по эффективности терапевтических подходов (эстрогены, вазоактивные препараты, физиотерапия, эндометриальное «скретчинг»-вмешательство, внутриматочное введение G-CSF, PRP, клеточная терапия).

Результаты. Большинство работ указывает на снижение частоты наступления беременности при толщине эндометрия <7 мм, однако описаны случаи успешной имплантации и при меньших значениях при наличии благоприятной структуры и рецептивности. Среди причин «тонкого» эндометрия доминируют внутриматочные вмешательства, хроническое воспаление, сосудисто-гемодинамические нарушения и гормональные факторы. Наиболее перспективными направлениями коррекции считаются стратегии, улучшающие ангиогенез и микроциркуляцию, а также локальные методы регенерации (PRP, G-CSF); результаты ERA/персонализированного переноса остаются дискуссионными.

Заключение. «Тонкий» эндометрий — мультифакторная проблема, требующая комплексной диагностики (морфология, воспаление, перфузия, маркеры рецептивности) и индивидуализированного лечения. Необходимы хорошо спланированные рандомизированные исследования с едиными критериями включения и клинически значимыми исходами (живорождение) для определения оптимальных алгоритмов ведения пациенток.

Ключевые слова: тонкий эндометрий; рецептивность эндометрия; окно имплантации; повторные имплантационные неудачи; ЭКО; доплерометрия маточных артерий; PRP-терапия.

YUPQA ENDOMETRIY VA ART/IVF DASTURLARIDA IMPLANTATSIYA MUVAFFAQIYATSIZLIKLARI: DIAGNOSTIK MEZONLAR, RETSEPTIVLIK MARKERLARI VA ZAMONAVIY DAVOLASH YONDASHUVLARI

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Annotatsiya.

Dolzarblik. Bachadon omili bilan bog‘liq bepushtlik, jumladan “yupqa” endometriy va uning retseptivligi pasayishi, ART/IVF dasturlarida takroriy implantatsiya muvaffaqiyatsizliklarining muhim sabablaridan biridir. “Yupqa endometriy” uchun yagona chegaraviy mezonning yo‘qligi hamda implantatsiya “oynasi”ni aniqlovchi universal testning mavjud emasligi klinik qaror qabul qilishni murakkablashtiradi.

Maqsad. “Yupqa endometriy” diagnostikasi, ultratovush va molekulyar retseptivlik markerlari, shuningdek an‘anaviy va innovatsion davolash usullarining samaradorligi bo‘yicha dalillarni tizimlashtirish.

Material va usullar. Endometriy qalinligi va tuzilmasi (M-echo, trilinear ko‘rinish, klassifikatsiyalar), bachadon tomirlari gemodinamikasi, surunkali endometrit, molekulyar markerlar (LIF, VEGF, integrinlar, pinopodiyalar) hamda davolash yondashuvlari (estrogen terapiyasi, vazoaktiv vositalar, fizioterapiya, endometriy “scratching”, intrauterin G-CSF, PRP, hujayra terapiyasi) bo‘yicha manbalar tahlil qilindi.

Natijalar. Ko'pchilik tadqiqotlarda endometriy qalinligi <7 mm bo'lganda homiladorlik ko'rsatkichlari pasayishi qayd etiladi, biroq retseptiv tuzilma saqlanganda pastroq qiymatlarda ham muvaffaqiyatli implantatsiya holatlari uchraydi. Asosiy etiologik omillar: ko'p marotaba intrauterin muolajalar, surunkali yallig'lanish, perfuziya/gemodinamik buzilishlar va gormonal omillar. Angiogenez va mikrosirkulyatsiyani yaxshilovchi hamda regeneratsiyani kuchaytiruvchi usullar (PRP, G-CSF) istiqbolli; ERA/personalizatsiyalangan transfer bo'yicha natijalar bahsli.

Xulosa. "Yupqa endometriy" kompleks yondashuvni talab qiladigan multifaktorial holatdir. Klinik amaliyot uchun yagona algoritmi belgilash maqsadida bir xil mezonlarga asoslangan va "tirik tug'ilish" natijasini baholaydigan RCT tadqiqotlar zarur.

Kalit so'zlar: yupqa endometriy; endometriy retseptivligi; implantatsiya oynasi; takroriy implantatsiya muvaffaqiyatsizligi; IVF/ART; bachadon arteriyalari doppleri; PRP terapiya.

Introduction. In the current demographic situation in our country, the implementation of reproductive function is becoming one of the primary tasks. According to official data (Rosstat, 2015), the prevalence of female infertility in Russia is 224.2 per 100,000 women aged 18–49 years [1]. The uterine factor of infertility is one of the leading ones, and, according to Korneeva I.E. [2], pathological changes in the endometrium occur in 88% of infertility cases. For pregnancy to occur, it is necessary to have a good quality embryo, an endometrium of adequate thickness and receptivity, and their successful interaction during the implantation window. Implantation failures remain one of the unresolved issues in infertility treatment to date. Insufficient endometrial thickness and decreased receptivity during the expected "implantation window" are associated with repeated reproductive failures in in vitro fertilization (IVF) cycles [3].

Endometrial thickness is measured during transvaginal ultrasound examination and is defined as the maximum distance between the echogenic borders of the endometrium and myometrium in a plane drawn through the central longitudinal section of the body of the uterus.

Currently, there is no generally accepted definition of a "thin" endometrium, and different authors may understand different M-Echo values as the threshold. The literature presents varying data on the minimum endometrial thickness required during the "implantation window" for successful pregnancy. Most researchers currently consider an endometrium less than 7 mm thick to be "thin" and insufficient for pregnancy [4, 5], while values of 8–12 mm are defined as optimal for implantation [6]. However, the literature describes cases of pregnancy and subsequent live birth with a maximum endometrial thickness of 4 mm [7].

In their study, Uzbekistan specialists examined 2,334 ovarian stimulation cycles in patients with a "thin" endometrium. According to their data, an endometrial thickness of 7 mm or less was statistically significantly associated with a reduced pregnancy rate [8]. Other researchers, when comparing pregnancy rates in patients with an endometrial thickness of less than 7 mm and those with an endometrial thickness of 8 mm or more after transferring thawed embryos, also found results of 5% and 30.9%, respectively [9].

Based on the obtained ultrasound parameters, the endometrium can be classified, which will provide an idea of its readiness for implantation and, to a certain extent, adjust the patient's subsequent management tactics. Thus, a three-layered endometrium on the day of ovulation trigger administration is defined as receptive, or class A. The presence of a clear central echogenic line

during transvaginal sonography on the day of ovulation trigger administration is characteristic of class B endometrium. Non-receptive endometrium (class C) is defined as a homogeneous endometrium without layering [10].

According to the results of a systematic review and meta-analysis conducted by Kasius et al. [11] and including 1170 patients undergoing IVF treatment, “thin” endometrium (less than 7 mm) was observed in only 2.4% of cycles in which pregnancy occurred.

There are conflicting opinions in the literature regarding the optimal endometrial thickness for predicting pregnancy in patients with reproductive dysfunction. Some studies have not found a clear relationship between endometrial thickness and the likelihood of pregnancy [12].

In contrast, some authors consider endometrial thickness to be a factor in determining the likelihood of pregnancy. According to numerous studies, endometrial thickness can serve as a predictor of IVF outcomes and pregnancy, but experts have not reached a consensus regarding the threshold for endometrial thickness [13].

Dix et al. [14], after conducting a retrospective analysis of 35 cases of embryo transfer with an endometrial thickness of less than 6 mm, obtained only 3 (8.5%) cases of successful implantation, of which 2 (5.7%) resulted in the birth of live children, that is, the probability of pregnancy with a “thin” endometrium was very low. Similar data were obtained by researchers from Hong Kong [9], having studied the relationship between endometrial thickness in 136 patients with infertility undergoing IVF treatment. With an endometrial thickness of less than 7 mm, the pregnancy rate in patients in ovarian stimulation cycles was 3%, while in patients with an endometrial thickness of 8 mm or more, it was 28%. In the case of transfer of thawed embryos, the pregnancy rate in patients with an endometrial thickness of less than 7 mm was 5%, and in patients with a thickness of 8 mm or more, it was 30.9%. The differences obtained are statistically significant.

A group of Uzbekistan researchers [13], after studying 2,334 ovarian stimulation cycles in infertile patients, concluded that an endometrial thickness of 7 mm or less was significantly associated with a lower pregnancy rate. Endometrial thickness of less than 7 mm was observed in 6.9% of patients. Furthermore, when analyzing the data, the specialists found that the relationship between endometrial thickness and pregnancy rate was most pronounced in patients over 35 years of age, leading the authors to hypothesize the existence of mechanisms of endometrial aging and the possibility that this process negatively impacts the likelihood of pregnancy.

Check JH and Cohen R. [15] believe that “thin” endometrium in patients can be considered as an indication for embryo cryopreservation for transfer into the uterine cavity in cycles with greater endometrial thickness. Kasius A. et al. [11], after conducting a systematic review and meta-analysis, concluded that endometrial thickness should not be used as the only marker for canceling embryo transfer into the uterine cavity.

Of interest are the data on the relationship between the endometrial thickness and the outcomes of IVF programs in stimulated cycles and cycles of transfer of thawed embryos. According to the data of Check JH et al. [16], with an endometrial thickness of 4–5 mm, the pregnancy rate after transfer of native embryos was 10.6%, while in the cryoprotocol it was 27.2% ($p=0.079$). Zhang T. et al. [17], in a retrospective analysis of 1512 IVF cycles, came to the conclusion that the endometrial thickness in a “fresh” IVF cycle is a better predictor of reproductive outcomes in subsequent cycles

of transfer of thawed embryos than the endometrial thickness in the thawed embryo transfer cycle itself.

Researchers from Turkey [18], conducting a clinical study that included 175 patients with an endometrial thickness of less than 7 mm on the day of oocyte retrieval, concluded that the pregnancy rate did not have a statistically significant difference among patients with an endometrial thickness of ≥ 4 and < 5 , ≥ 5 and < 6 , ≥ 6 and < 7 mm. However, when comparing these patients with women whose endometrial thickness was ≥ 7 mm, the pregnancy rate was 26 and 51%, respectively ($p < 0.0001$), and the miscarriage rate was 31 and 17%, respectively ($p < 0.02$).

Despite numerous studies aimed at discovering and developing new diagnostic methods, there is still no universal, highly accurate test capable of determining endometrial receptivity during the "implantation window." In practice, doctors use accessible and simple methods, such as measuring the thickness and structure of the endometrium during an ultrasound examination.

Modern medical equipment allows for dynamic monitoring of endometrial growth during ovarian stimulation, hormone replacement therapy, and the natural cycle. For a long time, the only key characteristics determining the quality and readiness of the endometrium for implantation were endometrial thickness and its trilaminar structure. As equipment has improved, specialists have gained the ability to assess endometrial tissue volume and subendometrial blood flow. Spanish researchers [19] demonstrated in their study that no difference was observed between endometrial thickness in cycles with and without pregnancy. However, a statistically significant difference was found between endometrial tissue volume values in these patients.

Chen SL et al. [20] assessed not only the thickness of the endometrium but also its trilaminar structure in their study. According to their results, with a trilaminar structure of the endometrium, the pregnancy rate was 24.4%, even with a thickness of less than 7 mm, while in the absence of trilaminar structure, pregnancy did not occur.

Patients with a "thin" endometrium typically have similar medical histories. These are typically women who have undergone multiple intrauterine procedures, including hysteroscopies with curettage of the uterine walls, hysteroscopic resections, surgical termination of pregnancy, etc. These patients have reduced menstrual flow and a history of repeated implantation failures and spontaneous abortions in the early stages of pregnancy.

Among the main reasons leading to a decrease in the thickness of the endometrium, the following can be distinguished: frequent intrauterine interventions resulting in damage to the basal layer of the endometrium, chronic endometritis (CE), impaired hemodynamics of the uterine vessels, changes in hormonal levels leading to a decrease in estrogen levels.

Persistent inflammation in the uterine mucosa contributes to impaired endometrial receptivity, which can lead to implantation failure [21]. The literature contains data indicating that CE is the main cause of IVF failure in 30% of cases [22]. Some researchers, however, believe that CE is not a significant factor in implantation failure in IVF programs [23].

Long-term use of certain medications, such as clomiphene citrate with its antiestrogenic effect on endometrial receptors [24] and combined oral contraceptives (COCs) [25], according to the literature, leads to a decrease in endometrial thickness. Insufficient endometrial growth is often observed during ovarian stimulation. Endometrial growth may be weak due to insufficient estradiol secretion by the ovaries in response to stimulation, as well as due to the negative impact of extremely

high doses of estradiol in the case of an increased ovarian response to stimulation. However, insufficient endometrial thickness cannot be explained solely by low blood estrogen levels, since estrogen levels are significantly higher during ovarian stimulation cycles than in natural cycles [26]. It should be noted that among the leading factors negatively affecting the thickness and receptivity of the endometrium, hemodynamic disturbances in the uterine vessels stand out. Angiogenesis plays a key role in the formation of an endometrium that is structurally and functionally optimal for embryo implantation. The functional layer of the endometrium has a capillary vascular network, while the basal layer contains larger vessels – spiral arteries. As early as 1957, studies were published according to which, in the postovulatory period, contraction of these endometrial vessels occurs [27]. It can be assumed that this occurs to reduce blood flow and oxygen pressure during the "implantation window", since it is known that increased oxygen pressure with the formation of its active forms creates unfavorable conditions for implantation and embryo development [28]. A clear correlation between endometrial thickness and blood flow parameters in the uterine vessels was identified by researchers studying the dynamics of endometrial thickness in patients in ovarian stimulation cycles in the IVF program and in natural cycles [29]. Alfer J. et al. [30] showed that a decrease in the expression of $\beta 3$ -integrin, vascular endothelial growth factor (VEGF), leukemia inhibitory factor (LIF) and CD56 is associated with insufficient angiogenesis, which leads to suboptimal development of endometrial tissue.

According to the data presented in the literature, patients with a "thin" endometrium are characterized by high resistance in the uterine arteries, decreased expression of VEGF and poor growth of glandular epithelium [31]. In studies devoted to the study of the relationship between angiogenesis and the formation of the endometrium, much attention was paid to the study of VEGF, since it is considered one of the main factors regulating angiogenesis in the human endometrium. It was shown that high resistance to blood flow in the radial arteries contributes to a decrease in the growth of glandular epithelium and, as a result, leads to a decrease in the level of VEGF expression in the endometrium [4]. A.V. Lvova [32] describes in her work that in the pathogenesis of "thin" endometrium, the main role is played by dyschronic maturation of the endometrial glands against the background of depletion of its vascular network, asynchrony of maturation of pinopodia, compaction of the stromal component, as well as a decrease in the expression of some growth factors, such as LIF-R, CD34, VEGF-A. Maekawa R. et al. [3], when studying potential molecular mechanisms of repeated implantation failures in women with "thin" endometrium, came to the conclusion that such patients are characterized by the presence of aberrantly activated inflammatory elements and decreased regulation of genes responsible for metabolism and the cell's response to oxidative stress.

The endometrium is most receptive during the "implantation window," i.e., the probability of implantation is limited in time. An idea of the receptivity of the endometrium can be obtained from histological, ultrasound, immunohistochemical, and molecular genetic studies. One of the most studied markers of the "implantation window" are pinopodia—outgrowths on the surface of the endometrial epithelium that are detected by electron microscopy in the middle of the luteal phase [33]. It is believed that the initial stages of blastocyst adhesion to the endometrium occur on the surface of pinopodia. However, a number of authors believe that the formation of pinopodia is not a sufficiently accurate marker of the "implantation window" [34]. Individual determination of the

"implantation window" for a specific patient became possible with the advent of a diagnostic test for endometrial receptivity based on the analysis of the expression of 248 genes (endometrial receptivity assay – ERA). It is important to note that even with a thickness of less than 7 mm, the endometrium can be receptive; this was shown by the results of a study conducted by Indian researchers [35].

Among the treatment methods for women with infertility due to a thin endometrium, the most traditional and widespread is estrogen therapy [36]. In addition, low doses of acetylsalicylic acid, omega-3 fatty acids [37], vaginal sildenafil citrate [38], pentoxifylline, and vitamin E [39] have been widely used in clinical practice to increase the thickness of the endometrium and improve blood circulation in the uterine vessels.

Estrogen preparations are most commonly used for endometrial growth. Estradiol can be administered orally, transdermally, and vaginally. However, the primary metabolism of estradiol in the liver after oral administration means that the therapeutic effect is primarily due to the action of metabolites, which have significantly lower affinity for the α - and β -estrogen receptors. The advantages of transdermal dosage forms include the absence of first-pass metabolism through the liver, a less significant effect on the hemostatic system, and greater bioavailability. Currently, estradiol preparations for vaginal use are not registered in Russia. It is important to consider that the use of medium doses of estrogens is more effective than low and high doses [40]. At the same time, according to Russian researchers, in patients with severe endometrial growth retardation (less than 4 mm), critical underdevelopment of the endometrium (less than 5 mm) persisted by the end of the first week of estrogen administration, even with intensive estrogen support [41]. Endometrial growth can be supported by exogenous estradiol in hormone replacement therapy cycles and endogenous estradiol secreted by the ovaries in natural cycles and ovarian stimulation cycles.

Today, physical methods of treatment are widely used at the pre-conception stage of women with reproductive dysfunction and hypoplastic endometrium [42]. Shneiderman M.G. et al. [43] published data on a significant increase in the thickness of the endometrium in patients with a "thin" endometrium using the method of irrigation of the uterine cavity with a gas mixture.

It should be noted that local trauma (scratching) of the endometrium promotes an increase in the regenerative potential and has a positive effect on the pregnancy rate in IVF cycles [44]. Endometrial scratching can be performed both during office hysteroscopy, when longitudinal scratches are made along the posterior and lateral surfaces of the uterus with biopsy forceps, and during endometrial pipelle biopsy. The literature presents data showing that performing an endometrial biopsy in the cycle preceding embryo transfer has a positive effect on the outcomes of IVF programs [45]. Controlled trauma to the mucosa leads to a massive release of growth factors and cytokines, which contributes to the restoration of the structure and receptivity of the endometrium.

Unfortunately, some patients do not respond to the treatments described above, necessitating further research into effective and safe approaches to treating women with a thin endometrium. Surrogacy is often the only option for these patients to have children. However, this not only entails enormous financial costs but is also a difficult and, in some cases, morally unacceptable step for some women. The literature presents data on the use of priming human chorionic gonadotropin in the follicular phase of the menstrual cycle against the background of the use of estrogen preparations [46], gonadotropin-releasing hormone agonists in the luteal phase of the cycle, acupuncture,

neuromuscular electrical stimulation in biofeedback mode in order to increase the thickness of the endometrium [47].

Among the new methods aimed at increasing the thickness of the endometrium, one can highlight the intrauterine administration of granulocyte colony-stimulating growth factor, which contributes to an increase in the frequency of clinical pregnancy compared with placebo, especially among women in Asian countries [48].

Another promising method is the introduction of autologous platelet-rich plasma (Platelet-Rich Plasma (PRP)). The use of autologous PRP for the treatment of women with infertility due to a thin endometrium was first described in 2015 by scientists from China [49]. According to the results of the study by Tandulwadkar S. et al. [50], the use of PRP in the cycle of transfer of thawed embryos contributes to an increase in the thickness of the endometrium and an improvement in intrauterine blood flow. Other researchers have also demonstrated an increase in the effectiveness of IVF programs in patients with a thin endometrium during therapy with autologous PRP [51]. Chang Y. et al. [52] published the results of a study that included 64 patients with an endometrial thickness of less than 7 mm during hormone replacement therapy. Patients in Group 1 (n=34) received intrauterine infusion of autologous PRP prior to the transfer of thawed embryos while undergoing hormone replacement therapy; 30 patients constituted the control group. The implantation and clinical pregnancy rates in patients receiving autologous PRP therapy were statistically significantly higher than those in the control group (27.94% and 11.67%, $p < 0.05$; 44.12% and 20%, $p < 0.05$, respectively).

Recently, researchers have shown increased interest in exploring the potential of cell therapy for "thin" endometrium. The literature contains studies on the use of stem cells derived from a woman's menstrual blood and mesenchymal stem cells. Promising results were obtained in a study in which autologous stem cells derived from bone marrow were injected through uterine arterioles into patients with refractory endometrium and Asherman syndrome [53]. However, these studies describe isolated cases of success and are primarily used in the treatment of severe forms of Asherman syndrome.

Conclusion. In conclusion, it should be noted that, despite numerous studies dedicated to finding new ways to increase the effectiveness of IVF programs by enhancing the receptivity of the "thin" endometrium, this issue remains controversial and unresolved. The lack of a universal, accurate, and accessible marker of endometrial receptivity, coupled with the combination of multiple factors influencing the effectiveness of embryo-endometrial tissue interaction during the "implantation window," complicates the analysis and identification of the true causes of reproductive failure. Undoubtedly, conducting new research to find effective treatments for women with a "thin" endometrium is becoming an important task in restoring reproductive function during natural conception and IVF programs.

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