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OPTIMIZATION OF PREOPERATIVE PREPARATION IN WOMEN WITH THIN ENDOMETRIUM BASED ON DECIDUALIZED STROMAL CELLS

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Abstract. Thin endometrium remains a clinically significant problem in reproductive medicine because it is associated with impaired endometrial receptivity, implantation failure, recurrent reproductive loss, and reduced effectiveness of assisted reproductive technologies. Conventional treatment strategies, including estrogen administration, vasoactive therapy, and adjuvant pharmacologic support, may improve endometrial thickness in some patients, yet their efficacy remains inconsistent, especially in refractory cases. In recent years, growing attention has been directed toward regenerative and cell-based approaches aimed not only at increasing endometrial thickness but also at restoring morphofunctional competence. Among these, menstrual blood-derived mesenchymal stem cells and their decidualized stromal derivatives have emerged as especially promising because of their accessibility, low invasiveness of procurement, angiogenic activity, immunomodulatory properties, and ability to enhance the secretory profile of the endometrial microenvironment. Decidualization appears to potentiate stromal cell functionality by increasing the expression of implantation-related and proangiogenic mediators, thereby improving tissue remodeling, vascularization, and endometrial receptivity. Current evidence suggests that such approaches may be particularly relevant for women with recurrent implantation failure, chronic endometrial insufficiency, and poor response to standard hormonal regimens. At the same time, many aspects remain unresolved, including protocol standardization, patient selection, long-term safety, and the translation of promising preclinical findings into routine clinical practice. Thus, optimization of preoperative preparation in women with thin endometrium based on decidualized stromal cells represents a promising and biologically grounded direction that warrants further controlled investigation.

Keywords: thin endometrium, endometrial receptivity, decidualization, stromal cells, mesenchymal stem cells, menstrual blood-derived stem cells, angiogenesis, implantation failure, infertility, regenerative medicine.

ОПТИМИЗАЦИЯ ПРЕДОПЕРАЦИОННОЙ ПОДГОТОВКИ У ЖЕНЩИН С ТОНКИМ ЭНДОМЕТРИЕМ НА ОСНОВЕ ДЕЦИДУАЛИЗИРОВАННЫХ СТРОМАЛЬНЫХ КЛЕТОК

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Аннотация. Тонкий эндометрий остаётся одной из наиболее сложных и до конца не решённых проблем современной репродуктивной медицины, поскольку ассоциирован со снижением рецептивности эндометрия, нарушением имплантации, повторными репродуктивными потерями и уменьшением эффективности программ вспомогательных репродуктивных технологий. Традиционные методы лечения, включая эстрогенотерапию, вазоактивную терапию и различные адъювантные фармакологические подходы, способны увеличивать толщину эндометрия лишь у части пациенток, при этом в рефрактерных случаях их результативность остаётся ограниченной. В последние годы всё большее внимание уделяется регенеративным технологиям, направленным не только на увеличение толщины эндометрия, но и на восстановление его морфофункциональной полноценности. Особый интерес представляют мезенхимальные стволовые клетки менструального

происхождения и полученные на их основе децидуализированные стромальные клетки, обладающие ангиогенным, иммуномодулирующим и выраженным паракринным потенциалом. Децидуализация, по-видимому, усиливает функциональную активность стромальных клеток, повышая экспрессию проангиогенных и имплантационно-значимых медиаторов, что способствует улучшению васкуляризации, ремоделирования ткани и рецептивности эндометрия. Такой подход может иметь наибольшую ценность у пациенток с повторными неудачами имплантации, хронической эндометриальной недостаточностью и недостаточным ответом на стандартную гормональную коррекцию. Вместе с тем сохраняются нерешённые вопросы, касающиеся стандартизации протоколов, отбора пациенток, оценки отдалённой безопасности и внедрения полученных данных в реальную клиническую практику. В связи с этим оптимизация предоперационной подготовки у женщин с тонким эндометрием на основе децидуализированных стромальных клеток представляет собой перспективное и патогенетически обоснованное направление дальнейших исследований.

Ключевые слова: тонкий эндометрий, рецептивность эндометрия, децидуализация, стромальные клетки, мезенхимальные стволовые клетки, менструальные стволовые клетки, ангиогенез, неудача имплантации, бесплодие, регенеративная медицина.

YUPQA ENDOMETRIYGA EGA AYOLLARDA DESIDUALIZATSIYALANGAN STROMAL HUJAYRALARGA ASOSLANGAN OPERATSIYADAN OLDINGI TAYYORGARLIKNI OPTIMALLASHTIRISH

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Annotatsiya. Yupqa endometriy zamonaviy reproduktiv tibbiyotning dolzarb va murakkab muammolaridan biri bo‘lib qolmoqda, chunki u endometriyning reseptivligi pasayishi, implantatsiya muvaffaqiyatsizligi, takroriy reproduktiv yo‘qotishlar hamda yordamchi reproduktiv texnologiyalar samaradorligining kamayishi bilan bog‘liq. An’anaviy davolash usullari, jumladan estrogenoterapiya, vazoaktiv terapiya va turli farmakologik yordamchi yondashuvlar ayrim bemorlarda endometriy qalinligini oshirishi mumkin, biroq refrakter holatlarda ularning samarasi ko‘pincha cheklangan bo‘lib qoladi. So‘nggi yillarda nafaqat endometriy qalinligini oshirish, balki uning morfofunksional to‘laqonliligini tiklashga qaratilgan regenerativ va hujayraviy yondashuvlarga qiziqish ortib bormoqda. Ayniqsa menstrual qondan olingan mezenximal ildiz hujayralar va ulardan hosil qilingan desidualizatsiyalangan stromal hujayralar angiogen, immunomodulyator va kuchli parakrin xususiyatlari tufayli katta istiqbolga ega. Desidualizatsiya stromal hujayralarning funksional faolligini kuchaytirib, implantatsiya uchun muhim bo‘lgan hamda angiogenezni rag‘batlantiruvchi mediatorlar ekspressiyasini oshirishi, shu orqali to‘qima remodellanishi, vaskulyarizatsiya va endometriy reseptivligini yaxshilashi mumkin. Bunday yondashuv, ayniqsa, takroriy implantatsiya muvaffaqiyatsizligi, surunkali endometriyal yetishmovchilik va standart gormonal davoga sust javob beradigan ayollarda muhim ahamiyat kasb etadi. Shu bilan birga, protokollarni standartlashtirish, bemorlarni tanlash, uzoq muddatli xavfsizlikni baholash va istiqbolli preklinik natijalarni amaliy klinikotga tatbiq etish bilan bog‘liq qator masalalar hanuz ochiq qolmoqda. Shunday ekan, yupqa endometriyli ayollarda desidualizatsiyalangan stromal hujayralarga asoslangan operatsiyadan oldingi tayyorgarlikni optimallashtirish kelgusida chuqur o‘rganilishi lozim bo‘lgan istiqbolli va patogenetik asoslangan yo‘nalish hisoblanadi.

Kalit so‘zlar: yupqa endometriy, endometriy reseptivligi, desidualizatsiya, stromal hujayralar, mezenximal ildiz hujayralar, menstrual qondan olingan ildiz hujayralar, angiogenez, implantatsiya muvaffaqiyatsizligi, bepushtlik, regenerativ tibbiyot.

Introduction. Thin endometrium (TE) remains one of the most challenging and controversial conditions in modern reproductive medicine, particularly in the context of assisted reproductive technologies (ART). Despite the significant advancements in embryology and

implantation techniques, the role of the endometrium as a limiting factor in successful pregnancy outcomes has become increasingly evident. In clinical practice, it is not uncommon to encounter patients with adequate embryo quality but repeated implantation failure, where impaired endometrial receptivity appears to be the primary determinant [2,5,7]. Conventionally, thin endometrium is defined as an endometrial thickness of less than 7 mm during the peri-implantation period. This threshold has been associated with significantly reduced implantation rates, lower clinical pregnancy rates, and increased risk of early pregnancy loss [1,4,6]. According to recent data, up to 67% of implantation failures in ART cycles are linked to inadequate endometrial receptivity, which is closely correlated with its morphofunctional characteristics, including thickness, vascularization, and molecular signaling pathways. From a pathophysiological perspective, the development of thin endometrium is primarily attributed to damage of the basal layer, which contains the progenitor stem cell population responsible for cyclic regeneration of the functional layer. Such damage may occur following repeated intrauterine procedures, chronic endometritis, or ischemic injury, ultimately leading to impaired proliferation, reduced angiogenesis, and altered immune microenvironment. In our clinical observations, even when endometrial thickness reaches borderline acceptable values, implantation failure may still occur, suggesting that structural parameters alone are insufficient indicators of functional receptivity. This underscores the importance of exploring therapeutic approaches that not only increase endometrial thickness but also restore its biological functionality.

Current treatment strategies include hormonal therapy, vasoactive agents, platelet-rich plasma, granulocyte colony-stimulating factor (G-CSF), and various physical modalities. However, their effectiveness remains inconsistent, and no standardized treatment protocol has been universally accepted . Therefore, the search for innovative and biologically driven therapies continues. In recent years, regenerative medicine has introduced a paradigm shift in the treatment of endometrial insufficiency. Mesenchymal stem cells (MSCs), particularly those derived from menstrual blood (MenSCs), have demonstrated significant potential due to their accessibility, low immunogenicity, and strong paracrine activity. Importantly, their therapeutic effects are increasingly understood to be mediated not by direct differentiation but by secretion of bioactive molecules that regulate angiogenesis, inflammation, and tissue remodeling [2,8,21].

A key physiological process in endometrial preparation is decidualization, which involves the transformation of stromal cells into specialized secretory cells under hormonal influence. This process is essential for embryo implantation and early pregnancy maintenance. Decidualized cells exhibit enhanced secretion of cytokines, growth factors, and angiogenic mediators, suggesting that preconditioning MSCs through decidualization may significantly enhance their therapeutic efficacy. Thus, the present study aims to evaluate the role of decidualized stromal cells derived from menstrual stem cells in optimizing preoperative preparation in women with thin endometrium, focusing on both morphological restoration and functional improvement.

Materials and Methods. This study was designed as an experimental translational investigation integrating cellular, molecular, and in vivo approaches.

Menstrual blood-derived mesenchymal stem cells were obtained from reproductive-age women without gynecological pathology. Cells were isolated using density gradient centrifugation and cultured in Dulbecco’s Modified Eagle Medium supplemented with fetal bovine serum and antibiotics under standard conditions.

Cell characterization was performed using flow cytometry to confirm expression of MSC markers (CD44, CD73, CD90, CD105) and absence of hematopoietic markers. Additionally, immunofluorescence analysis was conducted to assess expression of stromal and epithelial markers. Decidualization was induced in vitro using a combination of estradiol, medroxyprogesterone acetate, and cyclic AMP over a 14-day period. Morphological changes were monitored microscopically, and gene expression analysis was performed using quantitative PCR. Angiogenic potential was evaluated through VEGF-A quantification and endothelial cell migration assays. Furthermore, a rat model of thin endometrium was established via mechanical injury to simulate clinical conditions. Animals were divided into four groups: control, untreated TE, TE treated with MenSCs, and TE treated with decidualized stromal cells (DSCs). Endometrial thickness, glandular

density, and vascularization were assessed histologically. Fertility outcomes were evaluated by counting implantation sites.

Results. The isolated MenSCs demonstrated classical mesenchymal morphology and phenotype, with high expression of CD44, CD73, CD90, and CD105. Notably, OCT-4 expression was significantly elevated, indicating strong stemness characteristics.

Following decidualization, cells exhibited pronounced morphological transformation from spindle-shaped to polygonal forms. This was accompanied by reduced proliferative capacity but markedly increased expression of decidual markers, including prolactin and IGFBP-1.

VEGF-A secretion was significantly higher in DSCs compared to MenSCs, indicating enhanced angiogenic potential. This was further supported by increased endothelial cell migration in vitro.

In vivo, both MenSCs and DSCs improved endometrial thickness and glandular structure. However, the most significant differences were observed in functional outcomes. DSC-treated animals demonstrated near-normal implantation rates, while untreated TE models showed less than 20% implantation success.

Table 1. Comparative Morphological and Functional Outcomes

Parameter	Control	TE	TE + MenSCs	TE + DSCs
Endometrial thickness (mm)	7.5 ± 0.5	3.2 ± 0.4	5.8 ± 0.6	6.9 ± 0.5
Gland density	High	Low	Moderate	High
VEGF-A expression	Baseline	Decreased	Increased	Significantly increased
Implantation rate (%)	90%	<20%	60%	85%

Discussion. The problem of thin endometrium remains one of the most controversial and insufficiently resolved challenges in reproductive medicine, despite the rapid evolution of assisted reproductive technologies. While numerous therapeutic strategies have been proposed, ranging from hormonal stimulation to regenerative approaches, the heterogeneity of clinical outcomes suggests that the underlying pathophysiology is far more complex than previously assumed [2,5,7]. Traditionally, emphasis has been placed on increasing endometrial thickness as the primary therapeutic target. However, accumulating evidence indicates that thickness alone is an insufficient surrogate marker of receptivity. In our clinical observations, patients may reach the so-called “acceptable” threshold of 7–8 mm yet still demonstrate repeated implantation failure. This inconsistency implies that morphological restoration does not necessarily equate to functional recovery. Similar conclusions have been reported in contemporary literature, where endometrial receptivity is increasingly viewed as a multifactorial phenomenon involving molecular signaling, immune tolerance, vascular remodeling, and stromal cell transformation [4,11,14]. In this context, the present findings align with the growing body of evidence suggesting that the therapeutic potential of mesenchymal stem cells is primarily mediated through paracrine mechanisms rather than direct cellular replacement. The increased secretion of angiogenic factors, particularly VEGF-A, observed in decidualized stromal cells supports the hypothesis that restoration of microcirculation plays a central role in endometrial recovery [2,8,21]. This is consistent with previous experimental studies demonstrating that impaired angiogenesis is a key determinant of implantation failure in thin endometrium.

Interestingly, when comparing different regenerative approaches, stem cell-based therapies appear to outperform conventional pharmacological strategies in terms of long-term functional outcomes. Hormonal therapies, including high-dose estrogen or GnRH agonists, primarily stimulate proliferation but do not adequately address the underlying vascular and immunological deficiencies. Moreover, their effectiveness is often limited in patients with receptor dysfunction or chronic endometrial damage . Similarly, vasoactive agents such as sildenafil or aspirin improve perfusion but fail to induce полноценную тканевую регенерацию.

Autologous platelet-rich plasma (PRP), another widely studied modality, provides a concentrated source of growth factors and has shown promising results in increasing endometrial thickness. However, its effects appear to be transient and highly variable across patients, likely due to differences in individual platelet activity and local tissue responsiveness [46,47]. In contrast, stem cells offer a more sustained and dynamic source of bioactive molecules, capable of adapting to the microenvironment. The comparative advantage of decidualized stromal cells observed in the present

study deserves particular attention. While undifferentiated MenSCs demonstrated moderate regenerative capacity, their decidualized counterparts exhibited significantly enhanced secretory activity and angiogenic potential. This suggests that preconditioning stem cells through physiological transformation may be a critical step in maximizing their therapeutic efficacy. From a mechanistic standpoint, decidualization induces profound changes in gene expression, including upregulation of prolactin, IGFBP-1, LIF, and HOXA10—molecules known to play essential roles in implantation and early pregnancy maintenance. Moreover, decidualized cells actively modulate immune responses, promoting a tolerogenic environment that facilitates embryo acceptance. This immunological aspect is often underestimated but may be crucial in cases of repeated implantation failure. At the same time, it would be overly simplistic to consider decidualization as a universal solution. There remain important unanswered questions regarding the extent to which in vitro decidualization replicates physiological processes occurring in vivo. It is plausible that artificially induced cells may lack certain regulatory feedback mechanisms present in the native endometrial environment. Additionally, variability in culture conditions, hormonal exposure, and donor characteristics may significantly influence outcomes. Another point that warrants critical consideration is the translational gap between experimental models and clinical application. While animal studies provide valuable insights into mechanisms of action, they do not fully replicate the complexity of human reproductive physiology. Factors such as endocrine regulation, immune heterogeneity, and patient comorbidities may significantly alter therapeutic responses. Therefore, caution should be exercised when extrapolating these results to clinical practice. From a practical standpoint, the use of menstrual blood-derived stem cells offers clear advantages over other sources such as bone marrow or adipose tissue. The non-invasive nature of collection, absence of major ethical concerns, and relatively high proliferative capacity make them particularly attractive for clinical use. However, standardization of isolation, expansion, and differentiation protocols remains a critical challenge that must be addressed before large-scale implementation.

Furthermore, safety considerations cannot be overlooked. Although mesenchymal stem cells are generally considered safe, concerns remain regarding uncontrolled differentiation, potential pro-fibrotic effects, and long-term oncological risks. While current evidence does not indicate significant adverse outcomes, long-term follow-up studies are still lacking. An additional dimension that deserves attention is the economic and logistical feasibility of such therapies. Advanced cell-based treatments require specialized laboratory infrastructure, skilled personnel, and strict regulatory oversight. This may limit accessibility, particularly in resource-constrained settings. Therefore, future research should also focus on simplifying protocols and reducing costs without compromising efficacy. Despite these limitations, the results of this study contribute to a growing paradigm shift in reproductive medicine. Rather than focusing solely on structural parameters, there is an increasing recognition that functional restoration of the endometrium is the key determinant of successful implantation. In this regard, decidualized stromal cells represent not merely a regenerative tool but a biologically active system capable of orchestrating multiple processes simultaneously, including angiogenesis, immune modulation, and tissue remodeling. From a clinical perspective, this approach may be particularly relevant for patients with refractory thin endometrium, repeated implantation failure, or history of intrauterine damage. In such cases, conventional therapies often reach a therapeutic plateau, and regenerative strategies may provide a viable alternative.

Conclusion. In conclusion, decidualized stromal cells derived from menstrual stem cells represent a promising and biologically advanced approach for optimizing preoperative preparation in women with thin endometrium. Their enhanced angiogenic and secretory properties contribute to improved endometrial receptivity and fertility outcomes.

The therapeutic effect appears to be mediated primarily through modulation of the microenvironment rather than direct cellular replacement, emphasizing the importance of paracrine mechanisms in regenerative medicine. While further research is undoubtedly required, the integration of stem cell biology with reproductive medicine holds considerable promise. The concept of functional preconditioning, as demonstrated through decidualization, may represent a crucial step toward personalized and mechanism-driven therapy. It is likely that future treatment

algorithms will incorporate a combination of approaches, including hormonal support, vascular modulation, and targeted regenerative interventions.

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