



THE ROLE OF STEM CELLS AND EXOSOMES IN RESTORING FEMALE REPRODUCTIVE FUNCTION: ADVANCES IN REGENERATIVE GYNECOLOGY

Mamadaliyeva Bakhora Khabibullayevna

Samarkand State Medical University, Samarkand, Uzbekistan

Abstract. Disorders of female reproductive function, including infertility, premature ovarian insufficiency, and endometrial pathology, represent a significant medical and social challenge. Traditional therapeutic approaches, such as hormonal treatment and assisted reproductive technologies, often fail to fully restore physiological reproductive function. In recent years, regenerative medicine based on stem cells and exosomes has emerged as a promising strategy for addressing these conditions.

The aim of this study is to analyze current evidence regarding the role of stem cells and exosomes in restoring female reproductive function. Mechanisms of action are explored, including angiogenesis, anti-apoptotic effects, immunomodulation, and regulation of the cellular microenvironment. Particular attention is given to mesenchymal stem cells, endometrial stem cells, and their exosomes, which contain biologically active molecules such as microRNAs.

The findings indicate that stem cells and their exosomes promote endometrial regeneration, improve ovarian reserve, and restore folliculogenesis. In vitro activation of dormant follicles represents a promising therapeutic approach. These results highlight the high potential of regenerative strategies and their role in advancing personalized medicine in gynecology.

Keywords: stem cells, exosomes, regenerative gynecology, infertility, ovarian reserve, endometrium, angiogenesis, immunomodulation, folliculogenesis.

РОЛЬ СТВОЛОВЫХ КЛЕТОК И ЭКЗОСОМ В ВОССТАНОВЛЕНИИ РЕПРОДУКТИВНОЙ ФУНКЦИИ У ЖЕНЩИН: СОВРЕМЕННЫЕ ДОСТИЖЕНИЯ РЕГЕНЕРАТИВНОЙ ГИНЕКОЛОГИИ

Мамадалиева Бахора Хабибуллаевна

Самаркандский государственный медицинский университет, Самарканд, Узбекистан

Аннотация. Нарушения репродуктивной функции у женщин, включая бесплодие, синдром истощения яичников и патологию эндометрия, представляют собой значимую медицинскую и социальную проблему. Традиционные методы лечения, включая гормональную терапию и вспомогательные репродуктивные технологии, не всегда обеспечивают восстановление физиологической функции репродуктивной системы. В последние годы регенеративная медицина, основанная на применении стволовых клеток и экзосом, открывает новые перспективы в лечении данных состояний.

Цель исследования. Анализ современных данных о роли стволовых клеток и экзосом в восстановлении репродуктивной функции у женщин. Рассматриваются механизмы действия, включая ангиогенез, антиапоптотические эффекты, иммуномодуляцию и регуляцию клеточного микроокружения. Особое внимание уделено мезенхимальным стволовым клеткам, эндометриальным стволовым клеткам и их экзосомам, содержащим биологически активные молекулы, такие как микроРНК.

Показано, что стволовые клетки и их экзосомы способствуют регенерации эндометрия, улучшению овариального резерва и восстановлению фолликулогенеза. Перспективным направлением является технология in vitro активации фолликулов.

Полученные данные свидетельствуют о высокой эффективности регенеративных подходов и их потенциале в персонализированной медицине.

Ключевые слова: стволовые клетки, экзосомы, регенеративная гинекология, бесплодие, овариальный резерв, эндометрий, ангиогенез, иммуномодуляция, фолликулогенез.

AYOLLARDA REPRODUKTIV FUNKSIYANI TIKLASHDA ILDIZ HUJAYRALAR VA EKZOSOMALARNING ROLI: REGENERATIV GINEKOLOGIYANING ZAMONAVIY YUTUQLARI

Mamadaliyeva Bahora Habibullayevna

Samarqand davlat tibbiyot universiteti, Samarqand, O'zbekiston

Annotatsiya. Ayollarda reproduktiv funksiyaning buzilishi, jumladan bepushtlik, tuxumdonlarning erta yetishmovchiligi va endometriy patologiyalari muhim tibbiy va ijtimoiy muammo hisoblanadi. An'anaviy davolash usullari, jumladan gormonal terapiya va yordamchi reproduktiv texnologiyalar har doim ham reproduktiv tizimning fiziologik faoliyatini to'liq tiklay olmaydi. So'nggi yillarda ildiz hujayralar va ekzosomalarga asoslangan regenerativ tibbiyot ushbu muammolarni hal etishda istiqbolli yo'nalish sifatida rivojlanmoqda.

Tadqiqot maqsadi. Ildiz hujayralar va ekzosomalarning ayollarda reproduktiv funksiyani tiklashdagi rolini o'rganishdan iborat. Ularning ta'sir mexanizmlari, jumladan angiogenez, antiapoptotik effektlar, immunomodulyatsiya va hujayra mikroatrofini tartibga solish tahlil qilinadi. Ayniqsa mezeximal va endometriyal ildiz hujayralar hamda ularning mikroRNK saqllovchi ekzosomalari muhim ahamiyatga ega.

Natijalar shuni ko'rsatadiki, ushbu usullar endometriy regeneratsiyasini yaxshilaydi, tuxumdon rezervini oshiradi va follikulogenezni tiklaydi. In vitro follikul aktivatsiyasi istiqbolli yo'nalish hisoblanadi. Ushbu yondashuvlar individual tibbiyot rivojida muhim o'rin tutadi.

Kalit so'zlar: ildiz hujayralar, ekzosomalari, regenerativ ginekologiya, bepushtlik, tuxumdon rezervi, endometriy, angiogenez, immunomodulyatsiya, follikulogenez

Introduction. Female infertility remains a major global health challenge, affecting approximately 10–15% of women of reproductive age. Among the most complex and therapeutically resistant forms are conditions associated with impaired endometrial receptivity, diminished ovarian reserve, and premature ovarian insufficiency [1,3]. Traditional therapeutic strategies, including hormonal stimulation, assisted reproductive technologies (ART), and surgical interventions, often fail to fully restore reproductive potential, particularly in cases involving structural or functional damage to reproductive tissues. In recent years, regenerative medicine has emerged as a transformative paradigm in gynecology, offering novel therapeutic approaches based on cellular and molecular repair mechanisms [4,6,8,10]. Stem cell-based therapies and exosome-mediated signaling are at the forefront of this revolution, providing innovative strategies for tissue regeneration, immunomodulation, and restoration of physiological function. Stem cells possess unique properties, including self-renewal, multipotency, and the ability to differentiate into various cell lineages [2,4]. These characteristics make them particularly suitable for regenerative applications in reproductive medicine [1,2,9]. Various types of stem cells have been investigated, including mesenchymal stem cells (MSCs), endometrial stem/progenitor cells, bone marrow-derived stem cells, and induced pluripotent stem cells (iPSCs). These cells can contribute to tissue repair through direct differentiation, paracrine signaling, and modulation of the local microenvironment. Parallel to stem cell research, exosomes have gained increasing attention as key mediators of intercellular communication [2,5,7]. Exosomes are nano-sized extracellular vesicles (30–150 nm) secreted by various cell types, including stem cells, and contain bioactive molecules such as proteins, lipids, mRNA, and microRNA. They play a critical role in regulating cellular processes, including proliferation, angiogenesis, apoptosis, and immune responses. The pathophysiology of reproductive disorders often involves impaired angiogenesis, chronic inflammation, fibrosis, and immune dysregulation. For instance, abnormal immune tolerance at the

maternal–fetal interface has been implicated in implantation failure and recurrent pregnancy loss, with regulatory T cells (Treg) playing a central role in maintaining immune homeostasis [3,5,6,7,10]. Therefore, therapies that can simultaneously promote tissue regeneration and modulate immune responses are of particular interest.

The aim of this study is to provide a comprehensive analysis of the role of stem cells and exosomes in restoring female reproductive function, focusing on their mechanisms of action, clinical applications, and future translational potential in regenerative gynecology.

Materials and Methods. This study is a narrative and analytical synthesis of current scientific evidence combined with a conceptual modeling approach to evaluate regenerative strategies in gynecology. The methodology is based on integrating experimental, clinical, and translational research data related to stem cell therapy and exosome-based interventions. Data sources include peer-reviewed studies on mesenchymal stem cells, ovarian stem cells, endometrial regeneration, and exosome-mediated signaling pathways. Particular emphasis is placed on studies involving human reproductive tissues and clinical outcomes. The analysis focuses on four key domains: stem cell sources and characteristics, mechanisms of action, clinical applications, and emerging technologies such as in vitro activation (IVA) of follicles and exosome-based therapy. Stem cell types analyzed include bone marrow-derived mesenchymal stem cells, adipose-derived stem cells, umbilical cord-derived stem cells, and endometrial stem/progenitor cells. Each type was evaluated in terms of differentiation capacity, immunomodulatory properties, and regenerative potential. Exosome analysis included characterization of cargo molecules, including microRNAs involved in angiogenesis (miR-21, miR-126), anti-apoptotic signaling (miR-214), and immune regulation. The role of exosomes in modulating Treg function and inflammatory pathways was also examined [1,7,8].

To structure the analysis, we developed a conceptual framework integrating clinical, cellular, and molecular parameters.

Table 1. Types of Stem Cells Used in Regenerative Gynecology

Stem Cell Type	Source	Key Properties	Clinical Applications
MSCs	Bone marrow	Immunomodulation, angiogenesis	Endometrial repair
ADSCs	Adipose tissue	High proliferation	Ovarian rejuvenation
UC-MSCs	Umbilical cord	Low immunogenicity	Infertility treatment
Endometrial stem cells	Endometrium	Tissue-specific regeneration	Endometrial restoration

Results. The analysis demonstrates that stem cell therapy significantly enhances reproductive tissue regeneration through multiple mechanisms. These include cellular differentiation, secretion of growth factors, promotion of angiogenesis, and modulation of immune responses. One of the key findings is the dominant role of paracrine signaling rather than direct differentiation. Stem cells release a wide array of cytokines, growth factors, and extracellular vesicles that collectively create a regenerative microenvironment. Exosomes derived from stem cells were shown to replicate many therapeutic effects of their parent cells. They enhance endometrial proliferation, promote vascularization, and inhibit apoptosis. In addition, exosomes contribute to immune regulation by promoting Treg expansion and suppressing pro-inflammatory pathways []. In ovarian tissue, stem cell therapy has been associated with increased follicular development and improved hormonal profiles. The concept of in vitro activation (IVA) of dormant follicles has shown promising results, particularly in patients with premature ovarian insufficiency.

Table 2. Mechanisms of Action of Stem Cells and Exosomes

Mechanism	Stem Cells	Exosomes
Angiogenesis	VEGF secretion	miRNA-mediated
Anti-apoptosis	Growth factors	miR-214, miR-21
Immunomodulation	Treg activation	Cytokine signaling

Furthermore, clinical studies indicate improved pregnancy rates following stem cell therapy, particularly in patients with thin endometrium or Asherman syndrome.

Discussion. The findings of this study highlight the transformative potential of regenerative medicine in gynecology. Stem cells and exosomes represent a paradigm shift from symptomatic treatment to restoration of physiological function [2,5,8,9]. One of the most important aspects is the immunomodulatory effect of these therapies. The maternal–fetal interface requires a delicate balance between immune tolerance and defense. Dysregulation of Treg cells has been implicated in implantation failure and recurrent pregnancy loss [3,6,9,10]. Stem cells and their exosomes can restore this balance by enhancing Treg function and suppressing inflammatory responses [1,4,7]. Another critical mechanism is angiogenesis. Adequate vascularization is essential for both endometrial receptivity and placental development. Stem cells promote angiogenesis through VEGF secretion and activation of endothelial cells [6,8]. The use of exosomes offers several advantages over cell-based therapy, including lower immunogenicity, easier storage, and reduced risk of tumor formation [2,3,5,9]. However, challenges remain in standardizing exosome isolation and ensuring reproducibility. The integration of regenerative therapies with assisted reproductive technologies may further enhance outcomes. For example, combining stem cell therapy with IVF may improve implantation rates in patients with poor endometrial receptivity [1,2,3,4]. Despite promising results, several limitations must be considered. These include variability in stem cell sources, lack of standardized protocols, and limited long-term safety data.

Conclusion. Stem cells and exosomes represent a highly promising approach for restoring female reproductive function. Their ability to promote tissue regeneration, enhance angiogenesis, and modulate immune responses positions them as key tools in the future of reproductive medicine. The integration of regenerative medicine with advanced technologies, including artificial intelligence and molecular diagnostics, may further enhance treatment outcomes. Future research should focus on large-scale clinical trials, standardization of protocols, and long-term safety evaluation. Ultimately, regenerative gynecology has the potential to redefine the management of infertility and significantly improve reproductive outcomes.

References.

1. Trounson, A., & McDonald, C. (2015). Stem cell therapies in clinical trials: Progress and challenges. *Cell Stem Cell*, 17(1), 11–22. <https://doi.org/10.1016/j.stem.2015.06.007>
2. Lai, R. C., Yeo, R. W. Y., & Lim, S. K. (2015). Mesenchymal stem cell exosomes. *Seminars in Cell & Developmental Biology*, 40, 82–88. <https://doi.org/10.1016/j.semcdb.2015.03.001>
3. Zhang, S., Zhu, D., Li, H., Li, H., Feng, C., Zhang, W., & Wang, H. (2019). Stem cell therapy for ovarian failure. *Stem Cell Research & Therapy*, 10, 61. <https://doi.org/10.1186/s13287-019-1165-6>
4. Santamaria, X., Massasa, E. E., Feng, Y., Wolff, E., & Taylor, H. S. (2011). Derivation of endometrial stem cells. *Journal of Clinical Endocrinology & Metabolism*, 96(2), 468–476.
5. Kawamura, K., Cheng, Y., Suzuki, N., Deguchi, M., Sato, Y., Takae, S., ... & Hsueh, A. J. (2013). Hippo signaling disruption and ovarian follicle activation. *Proceedings of the National Academy of Sciences*, 110(43), 17474–17479.
6. De Miguel-Gómez, L., López-Martínez, S., Campo, H., Francés-Herrero, E., Faus, A., Díaz, A., ... & Cervelló, I. (2020). Stem cells and reproduction. *Human Reproduction Update*, 26(1), 1–26.
7. Kalluri, R., & LeBleu, V. S. (2020). The biology and function of exosomes. *Science*, 367(6478), eaau6977. <https://doi.org/10.1126/science.aau6977>
8. Yoon, B. S., Kim, Y. K., Lee, J. W., Kim, Y. S., & Lee, H. S. (2014). Mesenchymal stem cell-mediated tissue repair. *Experimental & Molecular Medicine*, 46, e85.
9. Herraiz, S., Romeu, M., Buigues, A., Martínez, S., Gómez-Seguí, I., Díaz-García, C., & Pellicer, A. (2018). Autologous stem cell ovarian transplantation. *Human Reproduction*, 33(10), 1811–1819.

10. Gargett, C. E., Schwab, K. E., & Deane, J. A. (2016). Endometrial stem/progenitor cells. *Human Reproduction Update*, 22(2), 137–163.