Sarem Journal of Medical Research. Volume 11, Issue 3, Autumn 2026: 105- 107

Beyond Stem Cells: Are Extracellular Vesicles the Next Frontier in Regenerative Reproductive Medicine?

ARTICLE INFO

DOI: 1052547/sjrm.11.3.1

Article Type

Editorial letter

Editorial

Authors

AboTaleb Saremi[1,2 *]

1- Sarem Gynecology, Obstetrics and Infertility Research Center, Sarem Women's Hospital, Iran University of Medical Science (IUMS), Tehran, Iran.
2- Sarem Cell Research Center (SCRC), Sarem Women's Hospital, Tehran, Iran.

Corresponding Authors:
AboTaleb Saremi; Sarem Gynecology, Obstetrics and Infertility Research Center, Sarem Women's Hospital, Iran University of Medical Sciences (IUMS), Tehran, Iran.
Address: Sarem Women Hospital, Basij Square, Phase 3, Ekbatan Town, Tehran, Iran. Postal code: 1396956111, Phone: +98 (21) 44670888, Fax: +98 (21) 44670432.

Abstract: Regenerative reproductive medicine has evolved in recent years from a predominantly laboratory-based concept into one of the rapidly advancing areas of infertility research. Within this field, mesenchymal stem cells, pluripotent cells, and other cellular populations have attracted considerable attention because of their potential capacity for tissue repair, modulation of inflammation, regulation of immune responses, and restoration of tissue function. However, a deeper understanding of the mechanisms underlying the actions of these cells has raised an important question: Are the cells themselves the principal mediators of the therapeutic effects, or are these effects primarily mediated by the signals that cells deliver to their surrounding microenvironment? [1,2]

Keywords: Stem cells, Extracellular vesicles, Reproductive regenerative medicine.

Received: 03 September 2026
Accepted: 06 September 2026
e Published: 07 September 2026

Article History

[Downloaded from saremjrm.com on 2026-11-14]

[DOI: 1052547/sjrm.11.3.1]

Editorial

Introduction

Regenerative reproductive medicine has evolved in recent years from a predominantly laboratory-based concept into one of the rapidly advancing areas of infertility research. Within this field, mesenchymal stem cells, pluripotent cells, and other cellular populations have attracted considerable attention because of their potential capacity for tissue repair, modulation of inflammation, regulation of immune responses, and restoration of tissue function. However, a deeper understanding of the mechanisms underlying the actions of these cells has raised an important question: Are the cells themselves the principal mediators of the therapeutic effects, or are these effects primarily mediated by the signals that cells deliver to their surrounding microenvironment? [1,2]

In this context**,** extracellular vesicles (EVs) and, in particular, exosomes have increasingly attracted attention as important mediators of intercellular communication. EVs are membrane-enclosed structures capable of transporting a broad range of biological molecules, including RNAs, microRNAs, proteins, and lipids, between cells. Therefore, some of the regenerative effects attributed to stem cells may in fact result from the signals transferred by these vesicles. This concept may shift the paradigm of regenerative medicine from cell-based therapy toward cell-free therapy. The importance of this conceptual shift may be particularly pronounced in reproductive medicine, as many reproductive disorders are not merely caused by the absence or dysfunction of a particular cell type, but rather result from complex disturbances in intercellular communication, chronic inflammation, alterations in the tissue microenvironment, and impaired tissue regeneration. Recent studies have demonstrated that EVs are involved in processes such as gamete maturation, early embryonic development, endometrial receptivity, and implantation. For example, emerging evidence indicates that endometrium-derived EVs can be internalized by blastocysts and influence molecular pathways associated with embryonic development and implantation [3,4].

Furthermore, more recent evidence has highlighted the role of EVs in the bidirectional communication between the embryo and the endometrium. Uterine EVs exhibit distinct molecular cargoes during the peri-implantation period and may modulate processes such as cellular differentiation, migration, invasion, oxidative stress regulation, and embryonic development. There is also evidence suggesting that embryo- and endometrium-derived EVs may contribute to the regulation of lipid metabolism, mitochondrial function, and extracellular matrix remodeling during implantation. These findings not only demonstrate the biological significance of EVs but also suggest a potential therapeutic opportunity. If EVs are capable of transmitting some of the beneficial functions of stem cells, their therapeutic application may help overcome certain limitations associated with cell-based therapies, including concerns regarding the survival and behavior of transplanted cells, cellular heterogeneity, the possibility of phenotypic alterations, and the difficulty of standardizing cellular products. In this context, EVs may be considered natural and relatively targeted carriers for the delivery of bioactive molecules [5].

The potential of this approach for ovarian regeneration is also receiving increasing attention. Recent studies have demonstrated that EVs derived from mesenchymal stem cells may modulate inflammatory pathways associated with ovarian aging. In addition, a study published in 2026 reported that EVs derived from embryonic stem cells were associated with improvements in the estrous cycle and fertility, reductions in ovarian fibrosis, and attenuation of certain aging-related phenotypes in an animal model of ovarian dysfunction [6]. Despite this promising outlook, however, the biological appeal of EVs should not be confused with their clinical readiness. One of the major challenges in this field is the heterogeneity of EVs and the lack of complete standardization across their production, isolation, purification, characterization, storage, and dosing processes. EVs are not simple or uniform biological products; their cargo can be influenced by the cell type of origin, culture conditions, cellular age, metabolic status, and even environmental conditions. Consequently, two apparently similar EV preparations may differ substantially in their molecular composition and biological effects. Another important issue concerns the relationship between molecular effects and actual reproductive outcomes. In many studies, changes in gene expression, reductions in inflammation, or improvements in cellular parameters have been considered indicators of therapeutic success. However, in reproductive medicine, the ultimate endpoints should, as far as possible, be linked to clinically meaningful outcomes such as improved implantation rates, ongoing pregnancy, and live birth. From this perspective, the translation of EV therapy from cellular and animal models to human treatment still requires stronger evidence and more rigorous standards [6].

On the other hand, EVs should not be viewed merely as a cell-free version of stem cell therapies. Perhaps the most important future opportunity lies in the engineering of EVs. Modification of their molecular cargo, selective loading of RNA or proteins, surface modification of vesicles, and the use of appropriate delivery systems may enable EVs to be transformed from natural messengers into engineered therapeutic tools. Such an approach could potentially shift the field from conventional regenerative medicine toward

[Downloaded from saremjrm.com on 2026-11-14]

[DOI: 1052547/sjrm.11.3.1]

a form of precision regenerative medicine. Within this framework, a fundamental question arises for researchers: Will the future of regenerative reproductive medicine continue to belong to cells, or will cells increasingly be regarded simply as sources of signals that can be independently isolated, standardized, and delivered to patients?

The answer to this question remains unclear. Nevertheless, accumulating evidence regarding the role of EVs in embryo–endometrial communication, ovarian function, and infertility-related disorders suggests that these vesicles are not merely by-products of cellular activity; rather, they constitute part of the molecular language of communication among reproductive cells. Therefore, the next step in this field should not merely be the generation of additional studies demonstrating that EVs exert beneficial effects. What is currently needed most is the standardization of EV products, elucidation of targeting mechanisms, assessment of long-term safety, and design of clinical studies with meaningful and patient-centered endpoints.

Perhaps the future of regenerative reproductive medicine will not lie in administering increasing numbers of cells, but rather in gaining a more precise understanding of the signals that cells use to promote tissue regeneration and restore reproductive homeostasis. If this hypothesis is confirmed by future studies, EVs may represent an important bridge between stem cell biology and the next generation of regenerative therapies, a transition from cell delivery to signal delivery.

References

1. Saha S, Roy P, Corbitt C, Kakar SS. Application of Stem Cell Therapy for Infertility. Cells 2021;10:

2. Cacciottola L, Vitale F, Donnez J, Dolmans MM. Use of mesenchymal stem cells to enhance or restore fertility potential: a systematic review of available experimental strategies. Human reproduction open 2023;2023:hoad040.

3. Salomon C, Das S, Erdbrügger U, Kalluri R, Kiang Lim S, Olefsky JM et al. Extracellular Vesicles and Their Emerging Roles as Cellular Messengers in Endocrinology: An Endocrine Society Scientific Statement. Endocrine reviews 2022;43:441-68.

4. Meng F, Deng Y, Li W, Zheng A, Lu M, Xing H. Engineered extracellular vesicles: From design strategies to therapeutic applications. Extracellular Vesicle 2026;7:100104.

5. Chen K, Liang J, Qin T, Zhang Y, Chen X, Wang Z. The Role of Extracellular Vesicles in Embryo Implantation. Frontiers in endocrinology 2022;13:809596.

6. Zou C, Yang Z, Zou Y, Xiao H, Deng Y, Bai J et al. Extracellular vesicles derived from differentiated granulosa-like cells restore the ovarian function of rats with premature ovarian insufficiency. Stem cells translational medicine 2026;15:

[Downloaded from saremjrm.com on 2026-11-14]

[DOI: 1052547/sjrm.11.3.1]