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Mini-Review

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# Therapeutic potential of mesenchymal stromal cell-derived extracellular vesicles in obstetrics and gynecology

**Raisa A. Chilova, Ekaterina O. Golubenko, Maria V. Poznyak, Kseniia I. Lavrenteva, Natalia S. Zemlina, Jing Li, Xinyu Wang, Wei Liu**

**Raisa A. Chilova,** MD, PhD, Professor, Head of the Department of Obstetrics and Gynecology No. 1, Sechenov First Moscow State Medical University (Sechenov University), 8/2, Trubetskaya str., Moscow, 119048, Russia

**Ekaterina O. Golubenko,** MD, PhD, Assistant, Department of Obstetrics and Gynecology No. 1, Sechenov First Moscow State Medical University (Sechenov University), 8/2, Trubetskaya str., Moscow, 119048, Russia

**Maria V. Poznyak,** MD, Assistant, Department of Obstetrics and Gynecology No. 1, Sechenov First Moscow State Medical University (Sechenov University), 8/2, Trubetskaya str., Moscow, 119048, Russia

**Kseniia I. Lavrenteva,** MD, Assistant, Department of Obstetrics and Gynecology No. 1, Sechenov First Moscow State Medical University (Sechenov University), 8/2, Trubetskaya str., Moscow, 119048, Russia

**Natalia S. Zemlina,** MD, Assistant, Department of Obstetrics and Gynecology No. 1, Sechenov First Moscow State Medical University (Sechenov University), 8/2, Trubetskaya str., Moscow, 119048, Russia

**Jing Li,** PhD, Professor, State Key Laboratory of Reproductive Medicine, Nanjing Medical University, 140, Hanzhong Road, Nanjing, 210029, China

**Xinyu Wang,** PhD, Researcher, State Key Laboratory of Reproductive Medicine, Nanjing Medical University, 140, Hanzhong Road, Nanjing, 210029, China

**Wei Liu,** PhD, Researcher, State Key Laboratory of Reproductive Medicine, Nanjing Medical University, 140, Hanzhong Road, Nanjing, 210029, China

**ORCID numbers:** Raisa A. Chilova 0000-0001-6331-3109; Ekaterina O. Golubenko 0000-0002-6968-862X; Maria V. Poznyak 0009-0006-8217-0784; Kseniia I. Lavrenteva 0000-0002-6250-8171; Natalia S. Zemlina 0000-0001-6393-9961; Jing Li 0000-0001-8692-4981; Xinyu Wang 0000-0003-4918-4245; Wei Liu 0000-0003-2106-5180

**Correspondence to:** Raisa A. Chilova
E-mail: chilova_r_a@staff.sechenov.ru

**Contributors:** Raisa A. Chilova: conceptualization, methodology, writing – review and editing, supervision. Ekaterina O. Golubenko: methodology, writing – original draft. Maria V. Poznyak: conceptualization, data curation, investigation, writing – original draft, visualization. Kseniia I. Lavrenteva: data curation, investigation, visualization. Natalia S. Zemlina: data curation, investigation. Jing Li: formal analysis. Xinyu Wang: formal analysis. Wei Liu: formal analysis.
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## ABSTRACT

In recent years, mesenchymal stromal cell (MSC) therapy has been widely studied as a major trend in medicine. However, it faces several clinical limitations, including immune reactions, tumor risks, and low homing efficiency. Consequently, cell-

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free strategies using MSC-derived extracellular vesicles (MSC-EV), particularly exosomes, are being studied as an increasingly recognized safer alternative. This mini-review aims to summarize current preclinical and early clinical evidence on the therapeutic potential of MSC-EV in female reproductive disorders, with a particular focus on premature ovarian insufficiency and thin endometrium, and to outline the key translational challenges to their clinical application.

Preclinical and clinical data indicate that MSC-EV modify target tissue functions by transferring microRNA, proteins, and lipids. In chemotherapy-induced premature ovarian insufficiency models, MSC-EV restore folliculogenesis, increase anti-Müllerian hormone levels, and reduce granulosa cell apoptosis. In thin endometrium models, vesicles improve tissue regeneration and stimulate angiogenesis via the wingless-related integration site / β-catenin and mitogen-activated protein kinase / extracellular signal-regulated kinase (MAPK/ERK) pathway. Overall, MSC-EV serve as a viable cell-free option in reproductive medicine, though standardized protocols and robust clinical trials are still required.

**Key Words:** regenerative gynecology; exosomes; mesenchymal stromal cells; female infertility; premature ovarian insufficiency; diminished ovarian reserve; thin endometrium

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## Introduction

The management of reproductive disorders, such as premature ovarian insufficiency (POI) and refractory thin endometrium, remains a clinical challenge due to their complex etiologies and association with female infertility. Over the past decade, regenerative medicine has introduced approaches ranging from whole-cell therapies to cell-free exosome-based strategies [1].

In preclinical models, mesenchymal stromal cell (MSC) transplantation demonstrates clear therapeutic effects. In a chemotherapy-induced POI model, Park et al. reported first-cycle pregnancy rates of 60–100% depending on dose, with fertility maintained at 60–80% in subsequent cycles [2]. MSC also increase endometrial thickness and enhance receptivity [1]. However, direct MSC transplantation has notable limitations: donor variability, immune reactions, tumor risks, low in vivo survival, and embolization risks during systemic administration. Cryopreservation, standardization, and transport of live cells are logistically difficult [3]. These challenges have shifted focus toward cell-free alternatives, specifically MSC-derived extracellular vesicles (MSC-EV), which retain parental cell therapeutic properties with enhanced safety and stability [1, 3].

To date, most available reviews have usually considered either mesenchymal stromal cells or MSC-EV separately. As a result, they only rarely offer a direct and clinically relevant comparison between whole-cell and cell-free approaches, especially in the context of premature ovarian insufficiency and thin endometrium [3, 4]. This mini-review tries to address this gap. It

summarizes recent preclinical evidence and the first clinical data on MSC-EV in female infertility and also compares MSC and MSC-EV in terms of their efficacy, duration of effect, safety profile, and practical potential for clinical translation.

This review aims to critically compare the therapeutic potential and limitations of whole-cell MSC versus MSC-EV in female fertility restoration, to synthesize the current preclinical and clinical evidence on MSC-EV efficacy, and to outline the key translational challenges that must be addressed before clinical adoption. We reviewed original articles and clinical trials (2018–2025) identified through PubMed and Web of Science using keywords: “extracellular vesicles”, “exosomes”, “mesenchymal stromal cells”, “female infertility”, “premature ovarian insufficiency”, “diminished ovarian reserve”, “thin endometrium”.

## Mesenchymal stromal cells and their derived extracellular vesicles: a comparison of therapeutic characteristics

Extracellular vesicles (EV), including exosomes (30–150 nm) and microvesicles (100–1000 nm), mediate intercellular communication by transferring regulatory non-coding RNA (microRNA and long non-coding RNA), bioactive proteins, cytokines, and lipids [1]. Upon endocytosis, membrane fusion, or receptor binding, their cargo modulates target cell signaling. Therapeutic effects rely on paracrine regulation driving three core processes:

- Anti-apoptosis: MSC-EV mediate protective effects by modulating signaling pathways involved in cell survival and inhibiting pro-apoptotic cascades [5–7]. By regulating the balance of pro- and anti-apoptotic proteins, MSC-EV inhibit programmed cell death and promote tissue repair in reproductive models [6, 7].
- Angiogenesis: MSC-EV promote the formation of new microvascular networks by delivering bioactive cargo that stimulates endothelial cell proliferation, migration, and tube formation [8, 9]. Research indicates that the angiogenic capacity of these vesicles is influenced by the tissue source of the parental MSC, as well as the environmental conditions — such as hypoxia — during vesicle production, which enhance their ability to drive functional angiogenesis in damaged tissues [8, 9].
- Immunomodulation: macrophage polarization from the pro-inflammatory M1 to the anti-inflammatory M2 phenotype reduces tumor necrosis factor-$\alpha$ and interleukin (IL)-1$\beta$ while increasing IL-10 and transforming growth factor-$\beta$ [10].

Through these molecular mechanisms, MSC-EV reduce inflammation and apoptosis in ovarian tissue [3], while promoting angiogenesis and inhibiting fibrotic growth in endometrial dysfunction models [1]. However, their efficacy can be limited compared to whole-cell therapy. For instance, in the aforementioned study, Park et al. reported first-cycle pregnancy rates of 30–50% in the exosome group, with no pregnancies in subsequent cycles, whereas whole-cell MSC provided sustained effects [2].

Key advantages of MSC-EV include absence of nucleus, eliminating genetic integration and minimizing tumor risk, and low immunogenicity facilitating standardization and storage. Unresolved challenges include the lack of unified isolation and quality assessment protocols, complicating cross-study comparisons [3]. Ultimately, MSC and MSC-EV are complementary:

whole-cell therapy offers more sustained functional effects [2], while cell-free approaches provide superior safety and producibility [3]. The key differences between whole-cell MSC therapy and MSC-EV therapy are summarized in Table 1.

We conclude that neither modality is universally superior; rather, MSC and MSC-EV occupy distinct therapeutic niches defined by the trade-off between efficacy durability and safety.

## Preclinical efficacy of mesenchymal stromal cell-derived extracellular vesicles

Animal models demonstrate efficacy of MSC-EV derived from various tissues, including human umbilical cord MSC-EV (hUC-MSC-EV) and brown adipose tissue, in polycystic ovary syndrome, POI, and implantation failure (e.g., thin endometrium) [6].

Zhang et al. showed that brown adipose tissue-derived exosomes restore oocyte mitochondrial activity, increase primordial, secondary, and antral follicle counts, and increase litter sizes in aging mice [11]. In chemotherapy-induced POI models, Xiao et al. reported that hUC-MSC-EV minimize DNA double-strand breaks, increase the Bcl-2/Bax ratio, suppress granulosa cell apoptosis, and down-regulate IL-1β and IL-6 [7]. Ding et al. demonstrated that engineered hUC-MSC-EV carrying a phosphatidylinositol 3-kinase / protein kinase B / mammalian target of rapamycin (PI3K/Akt/mTOR) agonist restore the estrous cycle and reduce cystic follicles in polycystic ovary syndrome models, outperforming unmodified vesicles [12].

For endometrial applications, Lin et al. reported that an EV-enriched biocompatible hydrogel promotes endometrial repair, increases functional layer thickness, stimulates angiogenesis, and enables live births in rats with endometrial injury [13].

Beyond therapy, follicular fluid EV serve diagnostic roles. Hu et al. identified exosomal microRNA profiles correlating with follicle size and maturity, targeting follicle-stimulating hormone secretion and transforming growth factor-β pathways, suggesting utility as non-invasive biomarkers of oocyte competence [14].

Collectively, these preclinical data establish a robust mechanistic foundation for MSC-EV therapy across distinct reproductive pathologies. However, we note that the marked efficacy observed in homogeneous animal models must be interpreted cautiously, as human populations present far greater biological and etiological heterogeneity.

**Table 1.** comparative characteristics of whole-cell mesenchymal stromal cell and mesenchymal stromal cell-derived extracellular vesicles

| Characteristic | Whole-cell mesenchymal stromal cells | Mesenchymal stromal cell-derived extracellular vesicles |
|---|---|---|
| Therapeutic mechanism | Paracrine secretion with possible cellular persistence | Paracrine regulation (proteins, lipids) |
| Tumor risk | Potential risk | Low/minimal (acellular) |
| Immunogenicity | Variable | Low |
| Stability/storage | Difficult (requires cryopreservation) | High (stable, easier to store/transport) |
| Efficacy profile | Sustained functional effects | Transient (often requires repeated dosing) |
| Standardization | Complex (donor variability) | More feasible than cell therapy |

## Clinical efficacy of mesenchymal stromal cell-derived extracellular vesicles and related extracellular vesicle-based therapies

### Therapeutic effects of extracellular vesicles in endometrial pathology

While extensive preclinical data demonstrate promising regenerative effects of MSC-EV, the study by Ebrahimi et al. stands as a primary published clinical trial [15]. In this single-center randomized controlled trial the authors evaluated the effectiveness of intrauterine injection of placental MSC-EV in women with persistent thin endometrium during frozen embryo transfer cycles. By the transfer day, women treated with exosomes demonstrated a higher mean increase in endometrial thickness, but this difference was not statistically significant. However, MSC-EV administration was associated with fewer cycle cancellations due to insufficient endometrial response. Clinical pregnancy rates were 12.5% for women treated with exosomes and 6.6% among those who did not receive this intervention. No adverse events were reported [15].

Although these results did not reach statistical significance for the primary endpoint, the clinically meaningful reduction in cycle cancellations and the numerically higher pregnancy rates suggest a promising signal that warrants confirmation in larger multicenter trials.

### Therapeutic effect of extracellular vesicles in ovarian dysfunction

Ovarian dysfunction studies are currently limited to pilot trials and case reports, with a growing number of clinical investigations evaluating the efficacy of diverse EV-based therapeutic strategies [16–19]. Navarro et al. conducted a prospective randomized study comparing the intraovarian administration of autologous plasma-derived EV, platelet-rich plasma, and saline in women with diminished ovarian reserve [16]. Plasma-derived EV therapy was associated with improved ovarian reserve parameters, including follicle-stimulating hormone, luteinizing hormone, estradiol, anti-Müllerian hormone, and antral follicle counts, as well as enhanced reproductive outcomes, such as a higher number of metaphase II oocytes, elevated fertilization rates, and higher clinical pregnancy rates [16].

Complementing these findings, evidence from early clinical studies discussed in the reviews has further characterized the therapeutic potential of MSC-EV [18, 19]. Moustaki et al. emphasize in their comprehensive review that cell-free biological therapies, particularly exosomes, offer a promising non-hormonal approach to rejuvenating the ovarian microenvironment and supporting follicular viability [19]. Furthermore, Geng et al. provided evidence that EV administration could modulate the local ovarian microenvironment, potentially overcoming resistance to conventional hormonal stimulation [18]. Alongside these trials, the clinical feasibility of local autologous EV delivery is supported by case report, including a documented spontaneous pregnancy following the intraovarian injection of menstrual blood-derived exosomes in a patient previously unresponsive to standard stimulation protocols [17].

While these preliminary findings are highly encouraging due to their favorable safety profile, the current evidence base remains restricted to small-scale pilot studies. Consequently, these data are currently insufficient to support broad clinical recommendations, and further validation in larger, multi-center randomized controlled trials is essential to establish the durability of these effects and standardize dosing regimens.

### Prospects and challenges for mesenchymal stromal cell-derived extracellular vesicles therapy

Currently, MSC-EV should be considered as an alternative or adjunct to whole-cell MSC transplantation rather than a complete replacement [3]. While cell-free approaches avoid cellular therapy risks and provide non-hormonal, organ-preserving options in gynecology [1, 3], clinical evidence remains limited. To date, no Phase III randomized controlled trials have been published; available data are restricted to preclinical models, pilot Phase I/II studies, and clinical registries [6]. Standardized trials are required to establish predictable outcomes before MSC-EV can be translated into routine clinical practice.

In our view, the path to clinical translation hinges on resolving three interconnected challenges: the standardization of isolation and characterization protocols, the establishment of disease-specific dosing regimens, and the execution of adequately powered randomized trials. Until these milestones are achieved, MSC-EV will remain a promising but experimental modality.

## Conclusion

The reviewed evidence highlights the role of EV in modulating reproductive physiology and underscores their dual utility as non-invasive diagnostic tools and promising therapeutic agents for fertility disorders. While the preclinical rationale is compelling and early clinical signals are encouraging, we conclude that the field has not yet crossed the threshold from experimental promise to evidence-based practice. Concerted efforts toward standardization and rigorous clinical evaluation will determine whether MSC-EV fulfill their therapeutic potential in reproductive medicine.

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