Review

Evaluating the Role of Exosome Therapy in Reproductive Aging: A Narrative Review of Recent Advancements

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ABSTRACT: Introduction: Exosome therapy shows promise as a non-hormonal treatment to restore ovarian function and combat reproductive aging. This review aims to explore recent advances, mechanisms, and clinical potential of exosome therapy in reproductive aging. Methods: This narrative review explored advancements in exosome therapy for reproductive aging through a comprehensive literature search of PubMed, Embase, Google Scholar, and ClinicalKey, covering studies from 2015 to 2025. Using a structured search strategy with relevant MeSH terms and keywords. After applying inclusion and exclusion criteria focused on human studies with therapeutic relevance, 13 articles were selected. Key data were extracted and synthesized to highlight mechanisms, clinical potential, and future directions of exosome-based interventions in ovarian aging. Results: Thirteen human-focused studies were categorized into four themes: ovarian function restoration, exosomal biomarkers, therapeutic roles in reproductive diseases, and clinical applications. Exosomes especially MSC-derived enhanced ovarian regeneration through anti-apoptotic, anti-inflammatory, and metabolic pathways. Age-related changes in exosomal cargo showed strong diagnostic potential. Exosomes also demonstrated therapeutic effects in POI and PCOS and showed promise as low-immunogenic, cell-free nanocarriers for targeted reproductive-aging interventions. Conclusion: Exosome therapy is a promising, non-hormonal option for addressing reproductive aging, with potential for safe and effective clinical use.

KEYWORDS: *Artificial intelligence, exosome, premature ovarian failure, gynecology.*

Introduction

Reproductive aging in women leads to a decline in ovarian function, resulting in decreased fertility and the onset of menopause [1].

Traditional interventions, such as hormone replacement therapy (HRT), aim to alleviate menopausal symptoms but often carry significant risks and do not address the fundamental causes of ovarian aging [2].

Recent research has highlighted exosome therapy as a promising, non-hormonal strategy to rejuvenate ovarian function and potentially delay reproductive aging.

Exosomes are small extracellular vesicles secreted by various cell types, including stem cells, and play a crucial role in intercellular communication by transferring proteins, lipids, and nucleic acids between cells [3].

In the context of ovarian aging, exosomes derived from mesenchymal stem cells (MSCs) have demonstrated potential in enhancing ovarian function. For instance, a study treated ovarian cortex specimens from perimenopausal women with human umbilical cord MSC-derived exosomes, resulting in increased estrogen levels and upregulation of estrogen receptor-alpha expression [4].

Additionally, there was a decrease in apoptotic markers and an increase in cellular proliferation markers, suggesting that exosome therapy could effectively enhance estrogen production and modulate receptor sensitivity in premenopausal ovarian tissues [5].

Moreover, ongoing clinical trials are exploring the therapeutic potential of exosomes in addressing reproductive aging. One such study aims to evaluate the safety and efficacy of exosomes derived from human placental mesenchymal stem cells in women with premature ovarian insufficiency (POI) [6].

This interventional pilot study investigates whether intravenous injection of these exosomes can restore steroidogenesis, folliculogenesis, and support improvements in quality of life, resumption of menstruation, and reversal of infertility in patients with POI and diminished ovarian reserve [7].

While these findings are promising, challenges remain in translating exosome therapy into clinical practice. Issues such as large-scale production, standardization, and ensuring the safety and efficacy of exosome-based treatments need to be addressed. Nonetheless, the current body of research underscores the potential of exosome therapy as a novel approach to mitigate reproductive aging and improve female reproductive health [8].

This narrative review synthesizes recent advancements in exosome therapy for reproductive aging, highlighting key

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mechanisms, preclinical outcomes, and clinical potential to guide future research in this emerging field.

Methodology

This narrative review was conducted to explore recent advancements in exosome therapy for reproductive aging.

A comprehensive literature search was carried out across four major databases: PubMed, Embase, Google Scholar, and ClinicalKey.

The search targeted articles published between 2015 and 2025 and focused on both original research and review articles related to the role of exosomes in ovarian and reproductive aging.

Data Source

A comprehensive and systematic search was conducted across four electronic databases: PubMed, Embase, Google Scholar, and ClinicalKey to identify relevant literature on exosome therapy in reproductive aging. With input from a medical librarian, a structured search strategy was developed combining MeSH terms and free-text keywords such as *"exosomes"*, *"extracellular vesicles"*, *"ovarian aging"*, and *"reproductive aging"* (Table 1).

Filters were applied to limit the search to English-language studies published between 2015 and 2025, encompassing both review and original research articles. The search prioritized recent findings on the therapeutic implications of exosomes in ovarian function, reproductive decline, and aging-related fertility issues.

Table 1. Search Strategy Summary.

Database	Search Keywords / Strategy	Filters Applied	Notes / Results
PubMed	(("Exosomes"[Mesh] OR exosomes[Title/Abstract] OR "extracellular vesicles"[Title/Abstract]) AND ("ovarian aging"[Title/Abstract] OR "reproductive aging"[Title/Abstract]))	English, last 10 years, review+research articles	Retrieved 18 relevant articles; 6 selected based on relevance to exosome therapy in aging ovaries.
Embase	('exosome'/exp OR exosome:ti,ab OR 'extracellular vesicle':ti,ab) AND ('ovarian aging':ti,ab OR 'reproductive aging':ti,ab)	English, 2015-2025, human studies	Identified 20 articles; 4 unique and relevant studies included.
Google Scholar	"exosome therapy" "reproductive aging" review Also tried: "extracellular vesicles" "ovarian aging"	Custom range: 2015-2025. Sort by relevance	516 studies were identified. Screened top 50 results; 3 additional relevant studies included.
ClinicalKey	("exosome therapy" OR "extracellular vesicles") AND ("ovarian aging" OR "reproductive aging")	English only, review articles	Located 2 additional clinical perspectives and book chapters.

Study Selection

The initial search yielded a total of 846 articles, which were screened in three stages: title, abstract, and full-text review according to the PRISMA flowchart (Figure 1).

Studies were eligible for inclusion if they focused on the therapeutic role or mechanistic insights of exosomes or extracellular vesicles in the context of reproductive or ovarian aging. To focus on translational results, only human studies were considered.

Exclusion criteria included studies unrelated to aging, reproductive health, or exosome-based approaches, as well as non-English publications, conference abstracts, or those lacking clear scientific rigor.

Additionally, animal studies were excluded. Ultimately, 13 articles were selected for final synthesis.

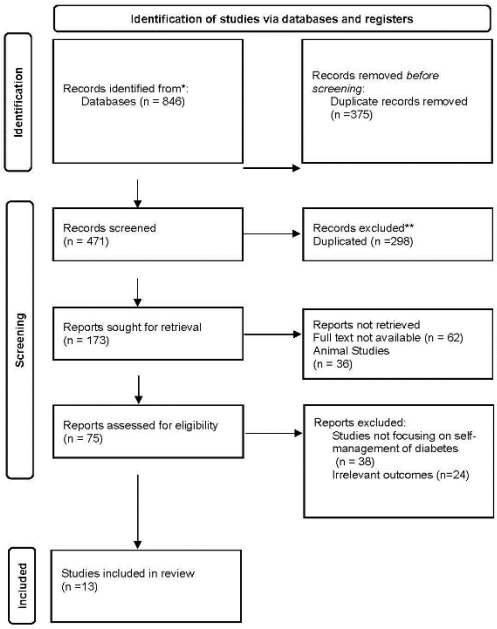

Figure 1. PRISMA flowchart for study selection.

Data Extraction

Key data were extracted from the included studies, focusing on the type of study, population/sample characteristics, year, core findings, and implications for reproductive aging. Articles were grouped by their methodological design (e.g., experimental studies, reviews, protocols) and thematic contribution, such as mechanisms of exosomal action, preclinical findings, or therapeutic outlook. Studies reporting novel applications, such as exosome-delivered microRNAs or stem cell-derived vesicles, were highlighted for their innovation and translational potential.

Data Synthesis

A narrative approach was used to synthesize findings from the selected studies. Articles were analyzed for recurring patterns in mechanisms of action, bio molecular pathways, and therapeutic outcomes. Emerging themes included the restorative potential of exosomes, miRNA delivery systems, and their comparative advantage over stem cell therapies. Studies were contextualized within the broader framework of reproductive longevity and cellular rejuvenation, aiming to identify both promising interventions and research gaps. The narrative is structured to guide readers through the scientific basis, experimental evidence, and clinical relevance of exosome therapy in reproductive aging.

Results

This narrative review includes 13 studies that examine the role of exosomes in female reproductive aging (Table 2).

Through thematic content analysis, findings were categorized into four major domains: (1) Exosome-Mediated Restoration of Ovarian Function, (2) Exosomal Biomarkers and Diagnostic Applications, (3) Exosomes in Reproductive Disease and Therapeutics, and (4) Exosome-Based Strategies in Reproductive Medicine. These categories collectively elucidate the promising roles of exosomes as diagnostic markers and therapeutic agents in managing age-related reproductive decline.

Table 2. Human-Focused Studies on Exosome-Based Strategies in Female Reproductive Aging.

Article Title	Authors	Year	Type	Country	Focus
Evaluation of the association between exosomal levels and female reproductive system and fertility outcome during aging: a systematic review protocol	Mobarak et al.	2019	Systematic Review Protocol	Iran	Protocol for studying the link between exosomes and reproductive aging
Physiological impact of extracellular vesicles on female reproductive system	Mobarak et al.	2019	Review	Iran	Reviews regenerative effects of exosomes on ovarian aging
Stem Cell Transplantation Improves Ovarian Function through Paracrine Mechanisms	Jiao et al.	2020	Original Research	China	Emphasizes exosomes as mediators in stem cell-driven ovarian rejuvenation
Knowledge Mapping of Stem Cell Therapy for Premature Ovarian Insufficiency	Cao et al.	2024	Bibliometric Analysis	China	Highlights rise in exosome-based ovarian restoration strategies
A Review on Stem Cell Therapy and Exosomes in Reproductive Medicine	Badalzadeh & Kharazi	N/A	Review	Iran	Summarizes the integration of exosomes into reproductive therapeutics
Therapeutic potential of exosomes/miRNAs in PCOS	Chen et al.	2022	Review	China	Discusses miRNA-based exosome therapy for PCOS-related dysfunction
Exosomes and Stem Cells in Degenerative Disease Therapy	Chang et al.	2018	Review	Taiwan	General framework for regenerative uses of exosomes
Exosome-based approaches in reproductive medicine	Badalzadeh et al.	~2023	Review	Iran	Reviews exosome applications in reproductive aging
Nano Drug Delivery in Female Genital Tract Disorders	van Staden et al.	2024	Review	South Africa	Discusses exosomes as nanocarriers in reproductive therapeutics
Exosome therapy for perimenopausal estrogen restoration	Alkhrait	2024	Original Research	Saudi Arabia	*Ex vivo* study showing estrogenic stimulation in aged ovarian tissue
Metabolomic profiling of follicular fluid exosomes	Gu	2024	Original Research	China	Identifies metabolic exosome markers of reproductive aging
Advances in exosome therapy for reproductive aging	Zhang	2024	Review	China	Discusses practical challenges and promise of exosome therapies
Exosomes in reproductive communication and diagnostics	Kowalczyk	2022	Review	Poland	Reviews diagnostic uses of exosomes in fertility and aging

10.12865/CHSJ.52.02.02

Exosome-Mediated Restoration of Ovarian Function

Mechanisms and Experimental Evidence

Stem cells can restore damaged ovarian tissue, but transplantation risks include tumorigenicity and difficulty obtaining consistent cell sources. Exosomes derived from mesenchymal stem cells (MSCs) or other stem cell types offer a cell-free alternative that reproduces many of the regenerative effects. Jiao et al. demonstrated that stem cell conditioned media and exosomes attenuated ovarian damage and mitigated fertility decline in female mice; their work highlighted exosomes as key mediators of the paracrine actions of transplanted cells [8].

Zhang's 2024 review on *exosome therapy in female reproductive aging* notes that exosomes from stem cells have comparable efficacy to parent cells but avoid risks associated with live-cell transplantation [10].

Exosomes deliver cargo (miRNAs, proteins, lipids) that inhibit apoptosis, reduce inflammation and fibrosis, and support angiogenesis. Badalzadeh & Kharazi highlight that exosomes stimulate cell proliferation, migration, oogenesis and embryo implantation and possess pro-angiogenic, anti-apoptotic and anti-inflammatory properties [11].

In an *ex vivo* study, Alkhrait (2024) treated perimenopausal ovarian cortex with exosomes derived from human umbilical cord MSCs. Exosome treatment significantly increased estrogen concentrations and estrogen-receptor-α expression, enhanced proliferative markers, and reduced apoptosis [12].

This suggests exosome therapy may restore hormone production in aged ovaries and could serve as a non-hormonal alternative to hormone-replacement therapy.

Advantages and Challenges

Exosomes are nano-sized (30-150nm) extracellular vesicles with a lipid bilayer and negative surface charge. They are natural facilitators of cell-to-cell communication and carry miRNAs, lipids and proteins to recipient cells. Their small size, high biocompatibility and stability in blood make them suitable for targeted drug delivery [9].

Exosomes derived from MSCs avoid ethical and tumorigenic concerns associated with stem-cell transplantation. Despite the mentioned advantages, production of high-quality exosomes is difficult. Zhang et al. emphasize that current manufacturing methods provide heterogeneous populations and scaling up is challenging [10].

Exosomes have low circulation half-life, potentially requiring higher or repeated doses. Concerns include immunosuppression, oncogenic cargo and difficulties in ensuring purity and stability [9].

Exosomal Biomarkers and Diagnostic Applications

Age-Related Changes in Exosomal Content

- **Metabolomic differences with aging**
- Metabolomic and molecular alterations with aging

Exosomal cargo undergoes significant alterations with increasing maternal age, particularly within the ovarian follicular microenvironment. These changes reflect underlying metabolic, hormonal, and cellular aging processes that directly influence oocyte quality and reproductive potential. Yanqiong Gu et al. conducted a metabolomic analysis of follicular fluid-derived exosomes from young and advanced-age women using gas chromatography-time-of-flight mass spectrometry (GC-TOFMS). The study identified 17 differentially expressed exosomal metabolites between the two groups. These metabolites were significantly associated with oocyte number, follicular function, and hormone levels, suggesting a close relationship between exosomal metabolic composition and ovarian reserve status. The authors concluded that exosomal metabolomic profiling of follicular fluid provides a sensitive tool for understanding age-associated nutritional and biochemical alterations in the ovarian microenvironment and may serve as a potential non-invasive biomarker of ovarian aging and reproductive capacity [13].

In addition to metabolomic changes, aging also influences exosomal lipid, protein, and RNA cargo. Multi-omics studies indicate that follicular fluid exosomes carry signaling molecules involved in oxidative stress regulation, mitochondrial function, and folliculogenesis, all of which decline with age. These molecular shifts contribute to reduced oocyte competence and impaired embryonic development [13].

- **EV alterations during senescence**

Beyond metabolomic profiling, aging-related modifications in extracellular vesicle biology have been widely documented. Mobarak et al. emphasized that cellular senescence significantly alters EV secretion dynamics and molecular composition, including exosomal RNA, proteins, and lipids. These changes are not merely passive biomarkers but may actively participate in intercellular signaling pathways that regulate reproductive aging and fertility decline [14].

Senescent cells tend to release EVs enriched in pro-inflammatory mediators and stress-associated molecules, which may disrupt granulosa cell function and impair oocyte maturation. Importantly, these EV-mediated changes can extend beyond the ovary, influencing systemic reproductive physiology and potentially contributing to age-related decline in fertility.

Recent evidence further supports the role of exosomal microRNAs and metabolites in regulating ovarian aging. Altered microRNA cargo within follicular fluid EVs has been proposed as a predictor of oocyte quality and developmental competence, reinforcing their diagnostic value in assisted reproductive technologies (ART) [14].

- **Diagnostic potential across reproductive fluids**

Exosomes are increasingly recognized as key mediators of intercellular communication within the male and female reproductive systems and as promising non-invasive diagnostic biomarkers [15].

These nano-sized vesicles (30-150nm) are present in multiple reproductive fluids, including semen, epididymal fluid, follicular fluid, oviductal secretions, and endometrial fluid, where they transport biologically active molecules such as proteins, lipids, DNA, and various RNA species.

Kowalczyk et al. describe exosomes as fundamental components of reproductive physiology that are released by a wide range of reproductive tract cells and circulate across both male and female reproductive environments. Their cargo is functionally active and plays a central role in regulating gametogenesis, sperm capacitation, acrosome reaction, fertilization, and embryo implantation. Importantly, exosomes reflect the physiological and pathological status of their originating cells because their molecular composition mirrors the intracellular environment from which they are derived. This characteristic makes them highly suitable as biomarkers for reproductive system disorders, including ovarian cancer, endometrial cancer, and prostate cancer [15].

Thus, exosomes represent a promising "liquid biopsy" for diagnosing fertility disorders and reproductive cancers.

Clinical Implications

Exosomal biomarkers could aid in early detection of diminished ovarian reserve or prediction of *in vitro* fertilization (IVF) outcomes, potentially guiding patient counselling. However, further standardization of isolation methods, normalization to protein content and large-scale clinical validation are necessary before routine clinical use [13,15].

Exosomes in Reproductive Disease and Therapeutics

Exosomal miRNAs and Molecular Pathways in PCOS

Chen et al. investigated the role of exosomal microRNAs (miRNAs) in PCOS pathogenesis and highlighted the potential influence of circadian rhythm disruption on circulating exosome profiles. Their findings suggest that altered circadian rhythms may modify exosomal secretion and cargo composition, thereby contributing to the development and progression of PCOS. Exosomes derived from PCOS models carry dysregulated miRNAs that target multiple intracellular signaling pathways, including PI3K/Akt, NF-κB, and AMPK/Nrf2, which are essential regulators of insulin signaling, inflammatory responses, and oxidative stress homeostasis [16].

Disruption of the PI3K/Akt pathway is closely linked to insulin resistance, a central feature of PCOS, while activation of NF-κB signaling contributes to chronic low-grade inflammation. Similarly, suppression of the AMPK/Nrf2 axis exacerbates oxidative stress, further aggravating ovarian dysfunction. Through these mechanisms, exosomal miRNAs serve not only as molecular mediators of disease progression but also as potential therapeutic targets for restoring metabolic and reproductive balance [16].

Circadian Rhythm Disruption and Exosome Dysregulation in PCOS

Recent evidence also highlights the interplay between circadian rhythm disturbances and exosome biology in PCOS. Circadian misalignment such as that induced by shift work or sleep disorders has been associated with

10.12865/CHSJ.52.02.02

increased risk of PCOS development. This dysregulation affects endocrine signaling and may alter exosome biogenesis, release, and molecular cargo composition.

Exosomes act as intercellular messengers that transmit circadian and metabolic signals between reproductive and metabolic tissues. Disruption of circadian regulation may therefore lead to abnormal exosomal communication, contributing to hormonal imbalance, insulin resistance, and ovarian dysfunction. This emerging concept links chronobiology with extracellular vesicle-mediated signaling in reproductive endocrinology and provides a novel framework for understanding PCOS pathogenesis [16].

Therapeutic Implications of Exosome/miRNA-Based Targeting in PCOS

The molecular insights provided by exosomal miRNA profiling suggest promising therapeutic applications. Modulation of exosome-derived miRNAs targeting key signaling pathways such as PI3K/Akt, NF-κB, and AMPK/Nrf2 may offer novel strategies for treating PCOS-related metabolic and reproductive dysfunctions. Experimental studies propose that restoring normal exosomal signaling could improve insulin sensitivity, reduce ovarian inflammation, and enhance follicular function.

However, despite growing evidence, the precise mechanisms linking circadian rhythm disruption, exosome dynamics, and PCOS pathophysiology remain incompletely understood. Further research is required to elucidate tissue-specific exosomal signatures and to validate their clinical utility as biomarkers or therapeutic agents in PCOS management [16].

These pathways offer targets for exosome/miRNA-based therapies, although mechanisms remain incompletely understood.

Premature Ovarian Insufficiency (POI)

Mesenchymal stem cell therapy is a promising approach for POI. Bibliometric analysis shows a rapid rise in publications on stem cell therapy for POI, particularly in China, and predicts that exosome-derived signalling pathways will be a key research focus [17].

Exosomes derived from MSCs can restore ovarian function in POI models and may circumvent risks associated with cell transplantation.

Other Reproductive Disorders

Exosome-based therapies have been explored for endometriosis, erectile dysfunction and asthenozoospermia. Badalzadeh & Kharazi highlight that exosomes have been successfully used to treat primary ovarian insufficiency and erectile dysfunction and suggest combining exosomes for treating endometriosis and sperm motility disorders [11].

Exosome-Based Strategies in Reproductive Medicine

Drug Delivery and Nanomedicine

Exosomes are ideal nanocarriers because they are naturally occurring, stable and can penetrate tissues. Their lipid bilayer and negative charge confer high biocompatibility and allow them to carry miRNAs, proteins and drugs. Exosomes can be loaded with small interfering RNA (siRNA), miRNA or therapeutic drugs via techniques such as electroporation, incubation, sonication or freeze-thaw cycles. As highlighted in *The Application of Nano Drug Delivery Systems in Female Upper Genital Tract Disorders*, exosomes from menstrual MSCs improved follicle development and stabilized estrogen cycles in rats.

However, exosome-based delivery may induce immunosuppression or tumorigenesis, and scaling up manufacturing remains difficult. Low circulation half-life means larger or repeated doses might be necessary [7,9,13,17]

Manufacturing and Translation

Standardization of isolation, characterization and cargo profiling is essential for clinical translation. Zhang's review emphasises that current production methods yield heterogeneous exosomes and make large-scale, high-caliber manufacturing challenging [10].

Purity and reproducibility must be improved to meet regulatory standards.

Because exosomes lack multipotency and differentiation potential, they do not engraft like stem cells and may require repeated administrations [9].

Nevertheless, their cell-free nature reduces ethical issues and safety risks. Future strategies may include engineered exosomes with targeted ligands or enhanced stability, or combination with biomaterials to prolong retention in the reproductive tract [13].

Integration into Reproductive Medicine

Exosomes are integral to maternal-embryo crosstalk. They mediate communication in follicular fluid, oocyte-granulosa cell complexes and the uterine environment, influencing oocyte quality and implantation [14].

Incorporating exosome science into fertility clinics may improve diagnostics and personalized therapies. On the other hand, the rise of exosome research necessitates updated curricula for reproductive medicine and allied health. Studies show that publications on stem cell and exosome therapy for POI are increasing rapidly, with exosome-mediated signalling anticipated to be a critical topic [17].

Training should cover exosome biology, therapeutic potential, isolation technologies and ethical considerations.

Discussion

This narrative review illustrates the current human-focused literature on exosomes in female reproductive aging, revealing a growing consensus on their therapeutic and diagnostic potential. Exosomes have emerged as central mediators of ovarian restoration, particularly due to their ability to transport functional molecules such as miRNAs, proteins, and lipids. These molecules contribute to tissue remodeling, endocrine support, and follicular development functions that become increasingly impaired with age.

The exploration of exosomes in female reproductive aging has promising aspects for both diagnostics and therapeutics. However, the field is still evolving, with ongoing debates and challenges that need to be addressed. Recent studies have elucidated the role of exosomes, particularly those derived from mesenchymal stem cells (MSCs), in restoring ovarian function [18].

These exosomes carry bioactive molecules such as miRNAs, proteins, and lipids that modulate key signaling pathways involved in folliculogenesis and ovarian cell survival [19].

For instance, exosomes from hypoxic MSCs have been shown to enhance angiogenesis in ovarian tissue, thereby improving the microenvironment for follicle development [6,20].

Additionally, exosomal miR-21-5p has been implicated in suppressing granulosa cell apoptosis by targeting the PTEN/Akt pathway, contributing to the preservation of the primordial follicle pool [6,21].

Despite promising preclinical data, several challenges impede the clinical translation of exosome-based therapies. Variability in isolation techniques leads to heterogeneity in exosome preparations, affecting reproducibility and efficacy [22].

Optimal dosing regimens and delivery methods for exosome therapies remain undefined, necessitating further pharmacokinetic and pharmacodynamics studies [23].

Long-term safety profiles of exosome treatments are not well-established [24].

While exosomes are generally considered less immunogenic than cell-based therapies, comprehensive immunological assessments are required. The classification of exosome products (as biologics, drugs, or advanced therapy medicinal products) varies across regulatory agencies, complicating the approval process [25].

Exosomes' inherent ability to deliver specific molecular cargo to target cells enables precise modulation of ovarian cellular functions [26].

Additionally, exosomes can be produced in substantial quantities and stored with minimal functional degradation, facilitating broader clinical applications [27].

However, it is imperative to recognize that exosome therapies are still in the nascent stages of clinical development, and their long-term efficacy and safety relative to established treatments like hormone replacement therapy (HRT) remain to be thoroughly evaluated [8].

Advancing this field necessitates a comprehensive understanding of the molecular mechanisms through which exosomes influence ovarian tissue. Research has indicated that exosomes derived from human umbilical cord mesenchymal stem cells (hucMSCs) can enhance follicular survival and development, potentially by modulating apoptotic pathways and reducing inflammation within the ovarian environment [28].

These findings suggest that hucMSC-derived exosomes may offer a novel strategy for preserving ovarian function, particularly in contexts such as chemotherapy-induced ovarian damage [4,29].

Identifying exosomal biomarkers predictive of ovarian reserve and responsiveness to therapy could further personalize treatment strategies [28].

Metabolomics analyses have revealed distinct differences in the exosomal content of

10.12865/CHSJ.52.02.02

follicular fluid between younger and older women. Notably, 17 metabolites were found to differ significantly, correlating with oocyte count and hormone levels. These findings underscore the potential of exosomal metabolites as biomarkers for reproductive aging, offering insights into the metabolic shifts that accompany diminished ovarian reserve [13].

However, rigorous, large-scale clinical trials are essential to assess the efficacy, safety, and optimal application parameters of exosome-based therapies across diverse populations.

A notable example is the VL-POI-01 study, designed to evaluate the safety and efficacy of human placental mesenchymal stem cell-derived exosome treatment in patients with premature ovarian insufficiency (POI) and diminished ovarian reserve [30,31].

Such studies are crucial for establishing evidence-based protocols and understanding the therapeutic potential of exosomes in clinical settings.

Establishing clear guidelines for the classification, production, and clinical application of exosome therapies will further facilitate their integration into standard medical practice. Standardization efforts are vital to ensure consistency, reproducibility, and safety across different therapeutic applications [25].

Conclusion

Exosome therapy represents a promising frontier in reproductive medicine.

Evidence from animal models and *ex vivo* studies shows that exosomes derived from stem cells or reproductive tissues can restore ovarian function, enhance hormone production and ameliorate age-related fertility decline.

Metabolomic profiling of follicular-fluid exosomes and changes in EV cargo during aging highlight their potential as biomarkers for early detection of reproductive aging.

Exosomal miRNAs offer therapeutic targets for PCOS and other reproductive diseases.

Despite these advances, translation to the clinic faces obstacles such as manufacturing heterogeneity, low bioavailability and safety concerns.

Rigorous clinical trials, standardized protocols and deeper mechanistic understanding are required before exosomes become routine tools for fertility restoration and diagnostics.

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Author Contribution

Conceptualization, E.AM. and H.M.T.; Methodology, H.M.T.; Investigation, E.AM. and H.M.T.; Data; Manuscript writing and initial draft preparation, E.A.M. and H.M.T.; Manuscript review and editing, E.AM. and H.M.T.; E.AM. and H.M.T. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare no conflict of interest regarding the publication of this paper.

Institutional Review Board

The study was conducted according to the guidelines of the Declaration of Helsinki. Ethical code was not applicable due to the study type.

Consent Statement

Not applicable.

Data availability

Data will be available via sending formal and rational request to the corresponding author.

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