REVIEW ARTICLE

The therapeutic potential of exosomes derived from mesenchymal stem cells for premature ovarian failure: A systematic review

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Abstract

This review evaluates mesenchymal stem cell-derived exosomes (MSC-Exos) for treating premature ovarian failure (POF). A comprehensive search was conducted across five databases, including PubMed, Embase, and Web of Science (WoS), yielding 17 English-language studies published between 2016 and 2025. Studies primarily using animal and in vitro models assessed the therapeutic effects and mechanisms of MSC-Exos from diverse sources. MSC-Exos significantly elevated estrogen levels, reduced follicle-stimulating hormone (FSH), increased antral follicle counts, and restored estrous cyclicity. Specifically, BMSC-Exos activated the PI3K/AKT pathway via miRNAs to suppress granulosa cell apoptosis; hUCMSC-Exos mitigated cellular senescence and autophagy; ADSC-Exos promoted follicular development through SMAD and SIRT1/FOXO1; PMSC-Exos attenuated ROS damage by improving mitochondrial function; AFSC-Exos together with MenSC-Exos enhanced oocyte maturation via the P53 pathway. Notably, perinatal exosomes showed 18–32% greater efficacy in functional recovery than adult-tissue counterparts with fewer doses. MSC-Exos present a promising therapeutic strategy for POF by targeting apoptosis, autophagy, angiogenesis, and oxidative stress. Perinatal-derived exosomes offer superior potential due to their non-invasive collection and minimal ethical concerns. Nonetheless, challenges pertaining to heterogeneity, long-term safety, and standardized manufacturing necessitate resolution through multicenter clinical trials to advance clinical applicability.. *(Afr J Reprod Health 2026; 30 [7]:124-138).*

Keywords Premature ovarian failure; Mesenchymal stem cells; Exosomes; treatment effect; treatment characteristics

Résumé

Cette revue évalue l'utilisation d'exosomes dérivés de cellules souches mésenchymateuses (MSC-Exos) pour le traitement de l'insuffisance ovarienne prématurée (IOP). Une recherche exhaustive a été menée dans cinq bases de données, notamment PubMed, Embase et Web of Science (WoS), et a permis d'identifier 17 études publiées en anglais entre 2016 et 2025. Les études, reposant principalement sur des modèles animaux et in vitro, ont examiné les effets thérapeutiques et les mécanismes d'action des MSC-Exos issus de différentes sources. Les MSC-Exos ont significativement augmenté les taux d'œstrogènes, réduit l'hormone folliculo-stimulante (FSH), accru le nombre de follicules antraux et rétabli la cyclicité œstrale. Plus précisément, les exosomes dérivés de cellules souches mésenchymateuses de la moelle osseuse (BMSC-Exos) ont activé la voie PI3K/AKT via des miARN afin de supprimer l'apoptose des cellules de la granulosa ; les exosomes dérivés de cellules souches mésenchymateuses du cordon ombilical humain (hUCMSC-Exos) ont atténué la sénescence cellulaire et modulé l'autophagie ; les exosomes dérivés de cellules souches mésenchymateuses du tissu adipeux (ADSC-Exos) ont favorisé le développement folliculaire via les voies SMAD et SIRT1/FOXO1 ; les exosomes dérivés de cellules souches mésenchymateuses placentaires (PMSC-Exos) ont réduit les dommages liés aux espèces réactives de l'oxygène (ROS) en améliorant la fonction mitochondriale ; les exosomes dérivés de cellules souches du liquide amniotique (AFSC-Exos), associés aux exosomes dérivés de cellules souches mésenchymateuses menstruelles (MenSC-Exos), ont amélioré la maturation ovocytaire via la voie P53. Il est à noter que les exosomes d'origine périnatale ont montré une efficacité de récupération fonctionnelle supérieure de 18 à 32 % à celle des exosomes issus de tissus adultes, et ce avec un nombre de doses plus faible. Les MSC-Exos constituent une stratégie thérapeutique prometteuse pour l'IOP en ciblant l'apoptose, l'autophagie, l'angiogenèse et le stress oxydatif. Les exosomes d'origine périnatale offrent un potentiel supérieur grâce à un prélèvement non invasif et à des préoccupations éthiques limitées. Néanmoins, des défis liés à l'hétérogénéité, à la sécurité à long terme et à la standardisation de la fabrication doivent être résolus au moyen d'essais cliniques multicentriques afin de favoriser une application clinique. *(Afr J Reprod Health 2026; 30 [7]: 124-138).*

Keywords: Premature ovarian failure; Mesenchymal stem cells; Exosomes; treatment effect; treatment characteristics.

Introduction

Premature ovarian failure (POF) is refers to a clinical syndrome in which women younger than 40 years develop ovarian dysfunction, which is mainly characterized by abnormal menstruation (amenorrhea or oligomenorrhea for at least 4 months), increased gonadotropin levels (an elevated follicle-stimulating hormone (FSH) level > 25 IU/L on two occasions > 4 weeks apart), and oestrogen-deficiency symptom[1].

The global overall prevalence of POF was 3.5%.[2,3] In addition, the age of onset is getting younger, about 1% of women under 40% and 0.1% of women under 30 are estimated to suffer from POF.[4] POF has become one of the main causes of infertility in women of childbearing age, it affects the quality of life of both patients and couples. POF is known to increase the risk of cardiovascular disorders[5], osteoporosis[6], cognitive decline,[7,8] and psychological disorders,[9-11] resulting in a reduced quality of life.

POF is a multifactorial and heterogeneous disease. Previous studies have suggested that POF cases are caused by genetic abnormalities, autoimmune factors, iatrogenic factors and environmental factors.[12-14] In the latest whole-genome sequencing data, at least 30% of POF cases are caused by genetic abnormalities, with staining abnormalities accounting for 10%-13%.[15] With the development of medical technology, the long-term survival rate of female cancer patients has been significantly improved through surgery, chemoradiotherapy, and other means. However, these treatments can lead to decreased ovarian function and even loss of fertility.[16-18] The POF induced by iatrogenic factors is more prominent in young patients.

As the etiology and pathogenesis of POF are complex and have not yet been clearly elucidated, there is no effective method to restore ovarian function. Hormone replacement therapy (HRT) is still the most common clinical treatment of POF. HRT is indicated to reduce the risk of osteoporosis, cardiovascular diseases, and urogenital atrophy and to improve the quality of life of women with POF.[16,19,20] However, HRT is considered unsafe in women with a history of breast cancer or ovarian cancer and its role of HRT in promoting fertility remains controversial. It also raises the risk of blood clots, cancer, strokes and other complications.[21,22] Therefore, there is an urgent need to explore new therapies for POF , and mesenchymal stem cell-derived exosomes (MSCs-Exos) transplantation is a promising treatment.

Numerous studies have reported the positive therapeutic effects of MSCs on POF patients through various mechanisms, including improving homing, differentiation, and paracrine stimulation. Recent research has attributed the regenerative potential of MSCs mainly to exosomes mediating paracrine effects.[23-25] MSCs-Exos can restore ovarian bioactivity and exhibit therapeutic effects because of their inherent regenerative properties.[23-25] As a vector, MSCs-Exos can also deliver miRNAs to target cells to transmit various signaling molecules.[26,27] Notably, products of MSCs-Exos from various sources of tissues show different levels of regenerative capabilities. In this review, we summarized the characteristics of MSC-Exos from different sources for POF treatment. Therefore we understand the advantages and disadvantages of MSC-Exos in the treatment of POF, and accumulate for further research on MSC-Exos.

Methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[28].

Data sources, search strategies, and search process

Database searches were performed across PubMed, Embase, Web of Science (WoS), Ovid Database, and the Cochrane Library, with no restrictions on publication date or language. No filters or limitations were applied, and the final search update occurred in July 2025. To ensure search comprehensiveness, keywords were extracted from study titles using the PICOS framework to construct search term combinations. Additionally, reference lists of relevant articles were manually screened to identify further eligible studies. The database-specific search strategies are detailed in Table 1

Table 1 : Database search strategy

Database	Search strategy	Filter	Number of Articles
PubMed	(((Primary Ovarian Insufficiency) OR (Premature ovarian failure) OR (premature ovary failure)) AND (Mesenchymal Stem Cells)) AND (Exosomes)	No filter set	55
Embase	('Primary Ovarian Insufficiency' OR 'Premature ovarian failure' OR 'premature ovary failure') AND ('Mesenchymal Stem Cells') AND ((Exosomes))	No filter set	48
Web Of Science	Refine results for (Primary Ovarian Insufficiency) OR (Premature ovarian failure) OR (premature ovary failure) (Topic) AND Mesenchymal Stem Cells (Topic) AND Exosomes (Topic)	No filter set	71
Ovid Database	(((Primary Ovarian Insufficiency) OR (Premature ovarian failure) OR (premature ovary failure)) AND (Mesenchymal Stem Cells)) AND (Exosomes)	No filter set	109
Cochrane Library	(Primary Ovarian Insufficiency) OR (Premature ovarian failure) OR (premature ovary failure) in Title Abstract Keyword AND Mesenchymal Stem Cells in Title Abstract Keyword AND Exosomes in Title Abstract Keyword - (Word variations have been searched)	No filter set	0

Inclusion and exclusion criteria

Inclusion criteria encompassed: (1) original peer-reviewed articles in English with open access; (2) studies specifically addressing the therapeutic effects of mesenchymal stem cell-derived exosomes on premature ovarian failure; (3) publications dated between 2016 and 2025 to capture the most recent advancements in mesenchymal stem cell-derived exosome therapy for premature ovarian failure; and (4) no limitations on study design.Exclusion criteria comprised: (1) reviews and case reports; (2) studies with incomplete data; and (3) duplicate publications.

Study selection and data extraction

All retrieved studies were initially imported into NoteExpress software for duplicate removal. Subsequently, two independent researcherszscreened studies based on the inclusion and exclusion criteria by reviewing titles and abstracts, followed by full-text assessment to finalize inclusions for this systematic review. Key data were then extracted into a Microsoft Excel spreadsheet, including: Study, Title, Nucleic acid effector molecules, MSCs type, Animal model, and Effects. These tasks were performed independently by the two researchers, with cross-verification conducted thereafter. Discrepancies were resolved through team discussions until consensus was achieved.

Ethic approval

As this is a retrospective study, no approval from an ethics committee or institutional review board was required for the research protocol, nor was informed consent necessary from study participants.

Results

Study selection and characteristics

Figure 1 presents the PRISMA flow diagram illustrating the study selection process. Per the search strategy, 283 studies were retrieved from electronic databases, supplemented by 9 from manual searches, yielding a total of 292 studies. Following duplicate removal, 149 studies remained. Of these, 111 were excluded after initial screening of titles and abstracts. Full-text eligibility assessments were then conducted on the remaining 38 studies, resulting in the exclusion of an additional 21. Ultimately, 17 studies were included in this systematic review. The screening workflow encompassed initial identification, duplicate exclusion, title-and-abstract screening, and full-text evaluation to select studies meeting inclusion criteria.

General characteristics of included studies

Table 2 summarizes the general characteristics of the included studies.

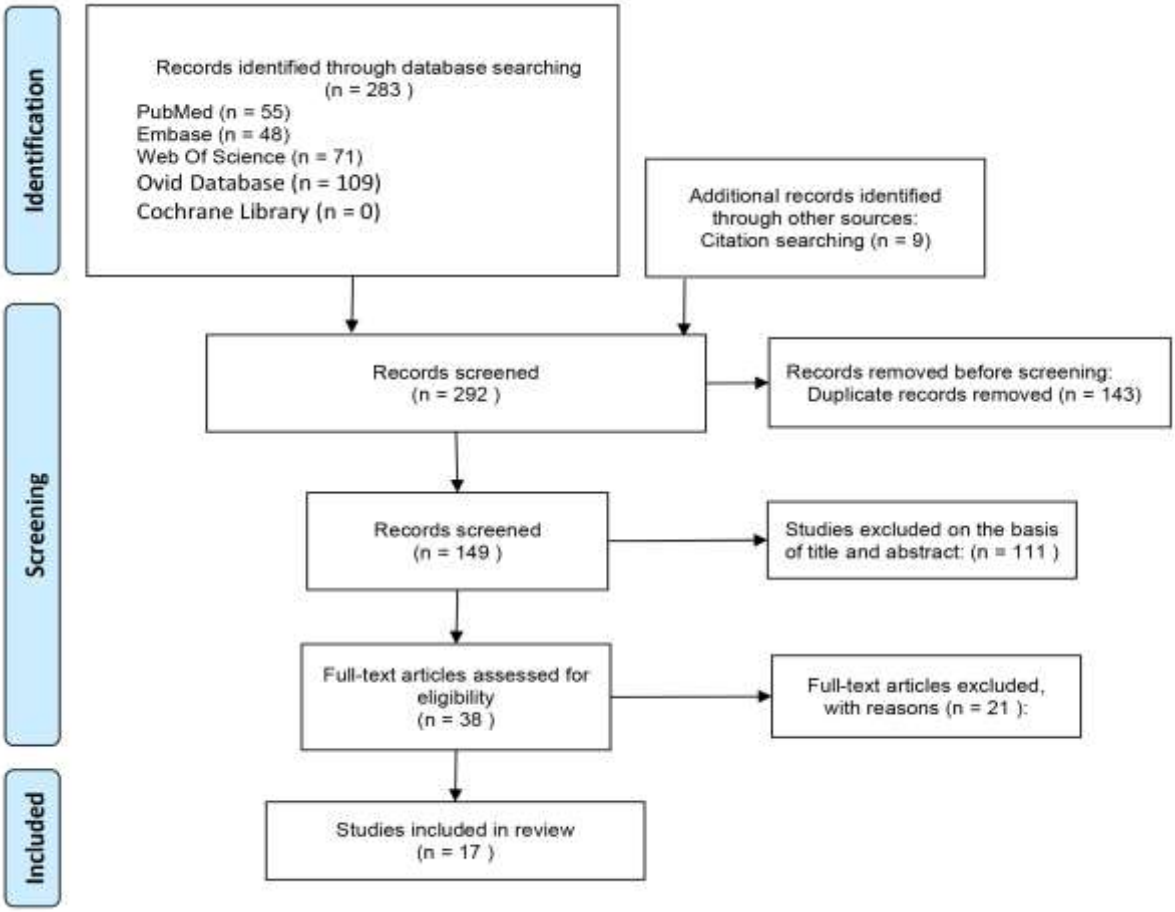

Figure 1: Flow chart of literature screening

Table 2: Basic characteristics of the included literature

Study	Title	Nucleic acid effector molecules	MSCs type	Animal Model	Effect
M.Yang et al. 2018 [29]	Bone marrow mesenchymal stem cell-derived exosomal miR-144-5p improves rat ovarian function after chemotherapy-induced ovarian failure by targeting PTEN	miR-144-5p	BMSC	Rat	Reduce gcs cell apoptosis and increase ovarian reserve via mediated PTEN inhibition to activate PI3K/AKT signaling
S.Chen et al. 2020 [30]	Similar Repair Effects of Human Placenta, Bone Marrow Mesenchymal Stem Cells, and Their Exosomes for Damaged SVOG Ovarian Granulosa Cells	miR-644-5p	BMSC	Human	Inhibit gcs cell apoptosis
B.Sunet et al. 2019 [31]	miR-644-5p carried by bone mesenchymal stem cell-derived exosomes targets regulation of p53 to inhibit ovarian granulosa cell apoptosis	miR-644-5p	BMSC	Mice	Inhibit gcs cell apoptosis by targets regulation of p53.
Qunwen Pan et al. 2019 [32]	Exosomes Derived from Mesenchymal Stem Cells Ameliorate Hypoxia/Reoxygenation-Injured ECs via Transferring MicroRNA-126	miR-126	BMSC	Mice	Enhance the survival and angiogenesis of damaged endothelial cells via activating the PI3K/Akt/enos pathway

Johnathon D Anderson et al. 2016 [33]	Comprehensive Proteomic Analysis of Mesenchymal Stem Cell Exosomes Reveals Modulation of Angiogenesis via Nuclear Factor-KappaB Signaling	BMSC-Exos	BMSC	HUVEC cell	Induce tubule formation in vitro and promote angiogenesis through the NF-kb signaling pathway
Ge Yang et al. 2024 [34]	Improving Granulosa Cell Function in Premature Ovarian Failure with Umbilical Cord Mesenchymal Stromal Cell Exosome-Derived hsa_circ_0002021	hsa_circ_0002021	hUCMSC	Mice	Alleviate the aging process of GC cells and improve ovarian function by regulating oxidative stress
B Xu et al. 2024 [35]	Repair effect of human umbilical cord mesenchymal stem cell-derived small extracellular vesicles on ovarian injury induced by cisplatin	huMSC-Exos	hUCMSC	Rat	Reduce gcs death by activation of PI3K/Akt signaling pathway and regulation of cellular autophagy
Y Li et al. 2024 [36]	Microfluidic Encapsulation of Exosomes Derived from Lipopolysaccharide-Treated Mesenchymal Stem Cells in Hyaluronic Acid Methacryloyl to Restore Ovarian Function in Mice	huMSC-Exos	hUCMSC	Mice	Rescue ovarian functions by increasing ovarian volume, improving the number of antral follicles and restoring fertility
Huang et al. 2018 [37]	Exosomes derived from human adipose mesenchymal stem cells improve ovary function of premature ovarian insufficiency by targeting SMAD	ADSCs-Exos	ADSC	Mice	Improved ovarian function of POI disease via regulation of the SMAD signaling pathway
Ding et al. 2018 [38]	HGF and BFGF Secretion by Human Adipose-Derived Stem Cells Improves Ovarian Function During Natural Aging via Activation of the SIRT1/FOXO1 Signaling Pathway	ADSCs-Exos	ADSC	Mice	Improve ovarian function via activating the SIRT1/FOXO1 signaling pathway to reduce
Yu Ren et al. 2023 [39]	Exosomes from adipose-derived stem cells alleviate premature ovarian failure via blockage of autophagy and AMPK/mTOR pathway	ADSCs-Exos	ADSC	Mice	Inhibit GC apoptosis and autophagy by AMPK/mTOR pathway
LiQian et al. 2024 [40]	Drug-free in vitro activation combined with ADSCs-derived exosomes restores ovarian function of rats with premature ovarian insufficiency	ADSCs-Exos	ADSC	Mice	Prevent the loss of follicles, promote follicular proliferation and inhibit apoptosis.
Bao Zhiyuan et al. 2024 [41]	Plasma-derived exosome miR-10a-5p promotes premature ovarian failure by target BDNF via the TrkB/Akt/mTOR signaling pathway	miR-10a-5p	PMSC	Rabbit	Regulate mitochondrial membrane potential to inhibit cell apoptosis
JinSeok et al. 2020 [42]	Placenta-Derived Mesenchymal Stem Cells Restore the Ovary Function in an Ovariectomized Rat Model via an Antioxidant Effect	PMSCs-Exos	PMSC	Mice	Restore the ovarian function via upregulated antioxidant factors
Duy-Cuong et al. 2024 [43]	Secretome from estrogen-responding human placenta-derived mesenchymal stem cells rescues ovarian function and circadian rhythm in mice with cyclophosphamide-induced primary ovarian insufficiency	PMSCs-Exos	PMSC	Mice	Reduce the defects of ovarian folliculogenesis and circadian rhythm and improve cytokines and growth factors associated with immunomodulation and angiogenesis
Z Geng et al. 2022 [44]	Human Amniotic Fluid Mesenchymal Stem Cell-Derived Exosomes Inhibit Apoptosis in Ovarian Granulosa Cell via miR-369-3p/YAF2/PDCD5/p53 Pathway	AFSCs-Exos	AFSC	Mice	Inhibit apoptosis of ovarian granulosa cells through the P53 signaling pathway
Hilda Rastegari et al. 2025[45]	Role of Menstrual Blood Stem Cell-Derived Secretome, Follicular Fluid, and Melatonin in Oocyte Maturation and Embryo Development in Polycystic Ovary Syndrome	MenSCs-Exos	MenSC	Mice	Promote oocyte maturation and inhibit cell apoptosis

This systematic review incorporated 17 English-language studies published between 2016 and 2025, all pertaining to mesenchymal stem cell-derived exosomes in the treatment of premature ovarian failure. Among these, 15 were animal experiments, 1 was a clinical trial, and 1 was an in vitro cellular study.

The studies encompassed: 5 on bone marrow mesenchymal stem cell-derived exosomes (BMSC-Exos), 3 on human umbilical cord mesenchymal stem cell-derived exosomes (hUCMSC-Exos), 4 on adipose-derived stem cell exosomes (ADSC-Exos), 3 on placental mesenchymal stem cell-derived exosomes (PMSC-Exos), 1 on amniotic fluid stem cell-derived exosomes (AFSC-Exos), and 1 on menstrual blood-derived mesenchymal stem cell exosomes (MenSC-Exos).

Effects of exosomes from different sources MSCs in treating POF

Mesenchymal stem cells

MSCs, a type of adult stem cells derived from mesoderm, are capable of self-renewal, multidirectional differentiation, and tissue reconstruction.[46] MSCs originate from a variety of locations across the human body, including the bone marrow, adipose tissue, connective muscle tissue, spleen, skin, amniotic membrane, placenta, umbilical cord, menstrual blood, and other tissues.[47] With the application of MSCs therapy, it has shown therapeutic effects in the treatment of neurological diseases, lung dysfunction, endocrine and metabolic related diseases, cardiovascular diseases and other diseases.[24,25] In recent decades, MSCs provide therapeutic advantages for POF via direct differentiation and paracrine actions, the latter of which is now regarded to be the most critical therapeutic mechanism.

The extracellular vesicles (like exosomes) secreted by MSCs carry a large number of regulatory factors (including growth factors, transformation factors, etc.), which can regulate the growth of collateral cells and biological processes and playing an important role in pathological cells in various disease processes. MSCs extracellular vesicles (MSCs-EVs), as one of the mediators of their signal transmission, play an important role in treating POF.

Exosomes

Exosomes are small vesicles with a diameter of 30-120 nm, which can be secreted by almost all types of cells.[48] The formation of exosomes begins in endosomes with inward budding of the limiting late endosomal membrane to generate intraluminal vesicles (ILVs) within a multivesicular endosome (MVE). Fusion of MVEs with the plasma membrane results in ILVs beingreleased to exosomes.[26] Exosomes are rich in proteins, lipids and genetic material, which are important tools for intercellular communication and regulating multiple intracellular biological processes.

Bone marrow mesenchymal stem cell-derived exosomes (BMSC-Exos)

Characteristics of BMSC

Bone marrow mesenchymal stem cells (BMSCs), a kind of adult stem cells with low immunogenicity, widely distributed in the bone marrow microenvironment. It is one of the most important sources of MSCs.[30] BMSCs are easy to isolate and expand in *vitro*. Compared with other MSCs, BMSCs have stronger heterogeneity, and their characteristics are closely related to the age or pathological status of the donor of LH level.The differentiation potential of BMSC will gradually decrease with increasing age.[49-51] BMSCs have received widespread attention due to their powerful potential of self-renewable, differentiation, and tissue or organ function reconstruction in regenerative medicine and tissue engineering.[52]

Effects and mechanisms of BMSC-Exos on POF

Dysfunction of ovarian granulosa cells (GCs) is pivotal in POF development[53]. Studies have shown that BMSC-Exos mainly improve ovarian function by inhibiting GCs cell apoptosis.[30,32] B.Sun et al[31] found that BMSC-Exos miR-644-5p could inhibit GCs cell apoptosis by targets regulation of p53. M.Yang et al showed that BMSC-Exos miR-144-5p could significantly restore the estrous cycle, increase the number of follicles, and regulate the reproductive hormone levels in POF rats, as it could reduce GCs cell apoptosis via targeting PTEN inhibition to activate PI3K/AKT signaling.[54]

Furthermore, BMSC-Exos can promote endothelial cell proliferation and angiogenesis. BMSC-Exos miR-126 is an important regulator of endothelial cell function and angiogenesis.[55] It can enhance the survival of endothelial cell and angiogenesis via activating the PI3K/Akt/eNOS pathway.[32] BMSC-Exos can also induce tubule formation *in vitro* and promote angiogenesis through the NF-kB signaling pathway.[33]

Human umbilical cord mesenchymal stem cells-derived exosomes (hUCMSCs-Exos)

Characteristics of hUCMSCs

hUCMSCs are derived from perinatal medical waste tissue - umbilical cord. There is no ethical controversy that this hUCMSCs collection process is non-invasive and harmless to human body. Compared with other sources, hUCMSCs from young perinatal period have fewer viral infections, higher value-added rate, and less ethical concerns.[56] Therefore, the human umbilical cord is a ideal source of MSCs. Those properties make hUC-MSCs a good choice for treating basic POF.

Effects and mechanisms of hUCMSCs-Exos on POF:

hUCMSCs-Exos showed excellent properties to improve ovarian function and fertility.[57,58] Abnormal autophagy, apoptosis, and aging can result in the decrease of GC cells. hUCMSCs-Exos can alleviate the aging process of GC cells. hUCMSCs-Exos hsa_circ_0002021 could ameliorate GC senescence in *vitro* and improve ovarian function in POF models by modulating oxidative stress and cellular senescence markers.[34] Furthermore, B Xu et al also showed that hUCMSCs-Exos could inhibit the autophagy of GCs to reduce cell death and increase the levels of hormone secretion, which recovery ovarian morphology, inhibit follicle hyperatretic and improved ovarian reserve capacity in cisplatin induced POF rats.[35] It indicates that hUCMSCs-Exos could not only prevent the occurrence of POF, but also may repair and reverse ovarian injury. Y Li et al also found that hUCMSCs-Exos could increase ovarian volume, the number of antral follicles and restored ovarian fertility to recover cyclophosphamide-induced ovarian failure.[36]

Adipose-derived stem cells-derived exosomes (ADSCs-Exos)

Characteristics of ADSCs

ADSCs, the high-quality biomaterial extracted from human adipose tissue, can be stably expanded under basic culture conditions, has low contamination risk, and low chance of immune rejection after transplantation.[59] They also have multiple advantages of extraction processes. Unlike BMSC, they can be easily isolated by minimally invasive methods.[4] ADSCs and its derivatives were found to regulate inflammation, promote tissue repair and wound healing, anti-nerve aging and promote new blood vessel growth.[60-62]

Effects and mechanisms of ADSCs-Exos on POF

Previous data in 2013 have demonstrated that hADSCs improved ovarian function in POF.[59] Huang *et al*[37] and Ding et al[38] confirmed that ADSCs-Exos could not only inhibited GC apoptosis, repair ovarian structure and endocrine function by activating the SMAD signaling pathway and SIRT1/FOXO1 signaling pathway, but also improve the microenvironment in ovarian tissue. Furthermore, Yu Ren et al found that ADSCs-Exos could inhibited GC autophagy by downregulation of AMPK/mTOR pathway.[39] In addition, the key factors of POF are the growth of follicular granulosa cells and the maturation of oocytes.[63] Interestingly, LiQian et al. concluded that ADSCs-Exos could regulate apoptosis-related protein BCL-2, Bax and Cleaved Caspase-3 expression to reduce the apoptosis of chemotherapy-induced follicle cells, and further promoting the development of the follicles.[40]

Placenta mesenchymal stem cells-derived exosomes (PMSCs-Exos)

Characteristics of PMSCs

The placenta is an organ that contains genetic material from two individuals (mother and fetus),[64] and it is usually discarded after full-term birth, so the acquisition of the placenta is a non-invasive procedure, safe and convenient.

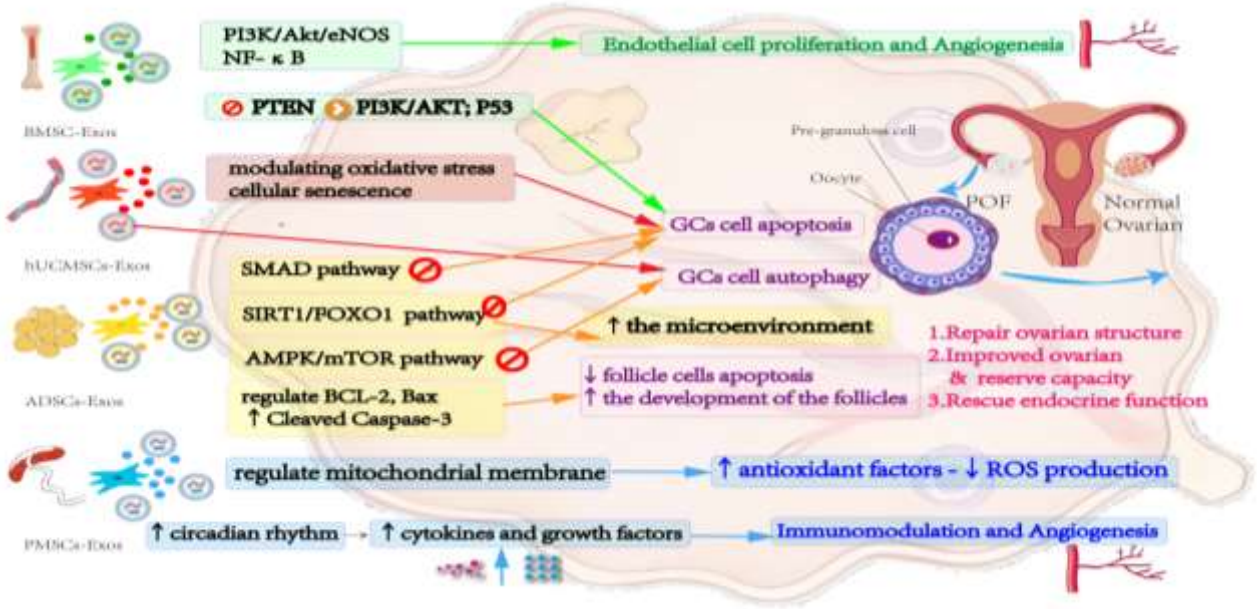

Figure 2: Effects of exosomes from different sources MSCs in treating POF

Different parts of the placenta contain abundant MSCs, such as facial features, decidua basement membrane, amniotic membrane, villi plate and Watton's glue.[65] They also have some remarkable advantages over other MSCs, due to their high differentiation, proliferation potential, survival, and expansion potential.[66] Meanwhile, they secreted more types of cytokines, including G-CSF, RANTES, IL-6, IL-8 , etc.[67] Its powerful regenerative ability makes them a broad application prospects for transplantation and regenerative medicine in the treatment of various diseases.[68,69]

Effects and mechanisms of PMSCs-Exos on POF

PMSCs are a new class of stem cells for transplantation with the potential to restore ovarian function in POF,[42] although it has been less studied in POF. PMSCs-Exos was shown to regulate relatively rare mechanism in other stem cells. PMSCs-Exos could regulate mitochondrial membrane potential to inhibit GC cell apoptosis.[41] Moreover, JinSeok et al. also found that it could upregulated antioxidant factors to inhibit ROS-induced GC cell apoptosis.[42] In addition, Duy-Cuong Le et al. found that it could reduce the defects of ovarian folliculogenesis and circadian rhythm and improve cytokines and growth factors associated with immunomodulation and angiogenesis.[43]

Other mesenchymal stem cells-derived exosomes

Amniotic Fluid Stem Cells-derived exosomes(AFSCs-Exos) are a group of stem cells in the amniotic fluid of pregnant women, characterized by low immunogenicity and the ability to express a variety of growth factors, such as epidermal growth factor and fibroblast growth factor.[70,71] Z Geng et al confirmed that AFSCs-Exos could inhibit apoptosis of ovarian granulosa cells through the P53 signaling pathway.[44] AFSCs-Exos have good therapeutic effects on many different diseases, like respiratory system diseases.[72,73] Menstrual Blood-Derived Mesenchymal Stem Cells (MenSCs-Exos) play a vital role in tissue repair and regeneration, including the repair and regeneration of the endometrium. It has shown that MenSCs-Exos could promote oocyte maturation and inhibit cell apoptosis.[74] Furthermore, there are many other source of mesenchymal stem cells in treating POF, like endometrial MSCs, and decidua MSCs.

Summary

It was demonstrated that MSC-Exos have therapeutic effect on POF, and its therapeutic mechanism is mainly related to the apoptosis of GC cells and the maturation process of oocytes. Different sources of MSCs have different therapeutic characteristics, which determine their potential for exploited. For example, UCMSCs-Exos, PMSCs-Exos and AFSCs-Exos have more development potential than BMSC-Exos and ADSCs-Exos. Because they were obtained using less invasive isolation techniques and out of the ethical debate

Discussion

This systematic review comprehensively synthesizes the therapeutic potential of MSC-Exos in treating POF. Literature analysis reveals that MSC-Exos from diverse sources demonstrate robust efficacy in ovarian repair, primarily through enhancing ovarian granulosa cell (GC) function, replenishing ovarian reserve, and bolstering fertility. Notably, BMSC-Exos exert their effects by targeting p53 and PTEN via miR-644-5p and miR-144-5p, thereby suppressing GC apoptosis and activating the PI3K/AKT signaling pathway to foster angiogenesis and restore ovarian function.[31,54] hUCMSC-Exos mitigate GC senescence and autophagy, while restoring ovarian volume and antral follicle counts; these exosomes exhibit both preventive and restorative capabilities against ovarian injury in cisplatin- or cyclophosphamide-induced POF models.[34-36] ADSC-Exos inhibit GC apoptosis and autophagy via activation of SMAD and SIRT1/FOXO1 pathways, concurrently modulating apoptosis-associated proteins—including BCL-2, Bax, and cleaved caspase-3—to facilitate follicular development. [37-40] PMSC-Exos distinctly modulate mitochondrial membrane potential and upregulate antioxidant factors, thereby attenuating ROS-mediated apoptosis and ameliorating factors related to immune modulation and angiogenesis.[41-43] Furthermore, exosomes from alternative sources, such as AFSC-Exos and menstrual blood-derived MenSC-Exos, suppress apoptosis and promote oocyte maturation through the p53 pathway.[44,45] Collectively, these observations underscore the multi-target reparative role of MSC-Exos in POF therapy, with variations in regenerative potency across sources; perinatal-derived exosomes (e.g., hUCMSC-Exos, PMSC-Exos, and AFSC-Exos) exhibit superior translational promise.

This systematic review incorporated 17 English-language original studies published between 2016 and 2025, encompassing MSC-Exos from diverse sources, including bone marrow, human umbilical cord, adipose tissue, placenta, amniotic fluid, and menstrual blood. These studies were primarily sourced from databases such as PubMed, Embase, and Web of Science, predominantly featuring animal models (e.g., rats, mice, and rabbits) and in vitro cellular experiments. They addressed chemotherapy-induced POF models (e.g., cisplatin and cyclophosphamide) as well as natural aging models. Inclusion criteria prioritized the source diversity of MSC-Exos, favoring experimental studies with well-defined mechanistic insights. For instance, animal model investigations by Sun et al. [31] and Yang et al.[29] furnished specific data on BMSC-Exos in murine POF; publications by Xu et al.[35] and Li et al.[36] centered on hUCMSC-Exos applications in rat models; and articles by Huang et al.[37] and Ding et al.[38] elucidated the therapeutic efficacy of ADSC-Exos in mice. Exclusion criteria encompassed non-English publications, descriptive studies devoid of mechanistic exploration, and MSC applications unrelated to POF. Overall, these studies exhibit high methodological quality, though predominantly preclinical, underscoring an evidentiary continuum from in vitro to in vivo models that lays a foundational groundwork for prospective clinical translation.

The therapeutic mechanisms of MSC-Exos in POF are predominantly mediated by paracrine signaling, encompassing multiple pathways including the inhibition of apoptosis, modulation of autophagy, mitigation of oxidative stress, and promotion of angiogenesis. Primarily, miRNAs encapsulated within MSC-Exos—such as miR-644-5p, miR-144-5p, and miR-126—target key signaling cascades, exemplified by the suppression of p53 and PTEN to activate the PI3K/AKT/eNOS pathway, thereby attenuating GC apoptosis and bolstering endothelial cell viability. [29,31,32] Furthermore, ADSC-Exos and hUCMSC-Exos suppress autophagy via downregulation of the AMPK/mTOR pathway while modulating the SIRT1/FOXO1 axis to ameliorate cellular

senescence.[34,38,39] Distinctively, PMSC-Exos orchestrate mitochondrial dynamics and upregulate antioxidant mediators to curtail reactive oxygen species (ROS)-induced injury.[41,42] Moreover, MSC-Exos enhance the ovarian niche by fostering immune modulation and neovascularization, as evidenced by NF-κB pathway-mediated tubulogenesis[33] and the orchestration of growth factors (e.g., G-CSF and IL-6) to augment folliculogenesis[43]. This mechanistic diversity arises from the inherent heterogeneity of MSC-Exos sources; for instance, perinatal-derived exosomes exhibit heightened cytokine secretion,[67] whereas bone marrow-derived variants prioritize differentiative capacity.[52] Prevailing evidence substantiates a tripartite regulatory paradigm—"miRNA-signaling axis–cellular behavior–organ function"—wherein: (1) the miR-144-5p/PTEN/PI3K-AKT and miR-126/PI3K-AKT/eNOS axes differentially curtail GC apoptosis and endothelial survival; (2) hsa_circ_0002021 collaborates with the SIRT1/FOXO1 pathway to attenuate oxidative stress and impede GC senescence; and (3) exosomal cargos, including TGF-β, HGF, and bFGF ligands, further engage SMAD2/3 and AMPK/mTOR signaling to rehabilitate the follicular milieu and diminish atresia rates. In essence, MSC-Exos orchestrate spatiotemporal duality via "multi-miRNA synergy coupled with protein signal amplification," surpassing the efficacy of singular recombinant factor supplementation. Contemporary investigations highlight that hypoxia-preconditioned MSC-Exos mitigate mitochondrial oxidative burden, while bone marrow MSC-Exos attenuate NLRP3 inflammasome activation to reinstate autoimmune POI homeostasis; collectively, these mechanisms reconstruct ovarian architecture, reinstate endocrine equilibrium, and ultimately ameliorate reproductive outcomes.

Clinical development of MSCs

This study elucidates the clinical potential of MSC-Exos in POF therapy, underscoring its profound implications for translational medicine. Foremost, MSC-Exos offer a novel cell-free therapeutic modality that may supplant hormone replacement therapy (HRT), thereby mitigating HRT-associated risks of thrombosis, malignancy, and cerebrovascular events.[21,22] Their low immunogenicity and high biocompatibility render them particularly apt for young cancer survivors or individuals with hereditary POF, circumventing HRT contraindications in those with a breast cancer history.[16,19] Per ClinicalTrials.gov data as of February 14, 2024, 21 clinical trials investigating MSCs and their extracellular vesicles for POF treatment have been registered, with 6 completed and 3 actively recruiting. Nonetheless, the predominant development paradigm relies on ovarian injections rather than intravenous administration. Consequently, advancing ovary-targeted MSCs or MSC-Exos via intravenous delivery bears substantial clinical relevance. Secondly, MSC-Exos from varied origins confer distinct advantages: hUCMSC-Exos, PMSC-Exos, and AFSC-Exos enable non-invasive procurement devoid of ethical quandaries, facilitating scalable production;[56,66] whereas ADSC-Exos permit minimally invasive harvesting and augment tissue regeneration.[59-62] These attributes extend to POF prophylaxis, exemplified by pre-chemotherapy deployment to safeguard ovarian integrity.[35,36] Moreover, MSC-Exos ameliorate POF comorbidities—encompassing cardiovascular disorders, osteoporosis, and psychiatric sequelae[5-11]—thereby elevating patient quality of life.[19,20] Ultimately, this investigation establishes a cornerstone for personalized therapeutics, such as tailoring exosome sources to patient demographics and etiologies (e.g., favoring perinatal origins in younger cohorts), thereby catalyzing the preclinical-to-clinical continuum and instilling renewed optimism for POF afflicted individuals.[3,21] Strategically, intravenous MSC-Exos administration obviates the hemorrhage, infection, and hilar trauma risks inherent to ovarian puncture, proving especially advantageous for fertility-preserving young oncology patients. For individualized paradigms, high-risk breast cancer cohorts should prioritize ethically unencumbered, low-viral-load umbilical cord or placental derivations; conversely, patients with pelvic adhesions benefit from menstrual blood-derived exosomes owing to their facile procurement and iterative autologous reinfusion feasibility. In synergy with assisted reproductive technologies (ART), preclinical evidence indicates that MSC-Exos augment post-chemotherapy oocyte yield and blastocyst formation in murine models, intimating their utility as ART preconditioning adjuncts—

albeit necessitating prospective trials to corroborate live birth efficacy. Regulatorily, exosomes classify as "acellular biologics," affording superior standardization vis-à-vis cellular therapies and alignment with FDA/EMA biosimilar frameworks, positioning them for expedited "fast-track" clinical ingress. Contemporary research buttresses MSC-Exos deployment in female reproductive senescence and accentuates synergistic ART augmentation.

Limitations of MSC-Exos researches

Shown by a large number of studies, MSC-Exos can recover the ovarian structure and function in POF treatment, but there are still some limitations in their research, and many challenges in their future development.

Homogeneity of MSC-Exos

In the process of obtaining MSC-Exos, there are strong individual differences among different sources, which leads to inconsistent biological activity of the obtained EVs. For example, the differentiation ability of BMSC-Exos is significantly decrease.[50,51] Additionally, the source of organization, culture conditions, separation methods, etc. can all affect therapeutic effect of MSC-Exos[75].

Long-term safety and validity evaluation of MSC-Exos

Although numerous preclinical studies have reported the good efficacy of MSC-Exos in the treating POF, many research is still concentrated on evaluating a single therapeutic effect. The efficacy evaluation of POF mainly focuses on observing the recovery of ovarian function and the improvement of fertility, with less attention to Long-term safety and validity evaluation. Moreover, MSC-Exos treatment is a biological therapy process, and the standardization of purity of exosomes is also very important for its safe application.

Production of MSC-Exos

As previously mentioned, MSCs from different sources and culture algebras will produce different exosome production effects, culture techniques, acquisition processes, and therapeutic effect. Therefore, it is a problem worth meditative that how to maintain a certain scale exosomes production. In a word, many studies have proved that MSC-Exos have the effect of treating POF, but it still has significant limitations in clinical application development and need further basic research on MSC-Exos as the foundation for future clinical translation.

Conclusion

In conclusion, MSC-Exos exhibit significant potential as a novel therapeutic approach for the treatment of POF. They have the potential to restore ovarian function and fertility, thereby delaying the progression of POF. Different sources of MSC-Exos possess unique characteristics and acquisition methods, influencing the challenges in clinical development and their potential applications. For example, AFSCs-Exos and PMSCs-Exos exhibit stronger differentiation abilities and can be obtained non-invasively, increasing their clinical development potential. However, clinical application faces challenges such as quality consistency, purity standards, and long-term safety and efficacy assessments. Therefore, we need further basic research of MSC-Exos on its extraction, purification and other process flows to ensure the rationality of clinical development. Finally, MSC-Exos hold great potential for clinical use, offering new hope for POF patients and others with various diseases

Author contributions

Chu-Qiao Chen: conception and design, data analysis, manuscript writing, interpretation and final approval of the manuscript. Xin-Run Wang: manuscript writing and interpretation. Xiao-Jing Zhao: manuscript writing, data analysis and interpretation. Liang Wang*: manuscript writing, administrative support, and final approval of the manuscript. All authors have read and approved the article.

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