

Application of mesenchymal stem cell therapy for premature ovarian insufficiency: Recent advances from mechanisms to therapeutics

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Abstract

The incidence of premature ovarian insufficiency (POI) is increasing worldwide, particularly among younger women, posing a significant challenge to fertility. In addition to menopausal symptoms, POI leads to several complications that profoundly affect female reproductive function and overall health. Unfortunately, current clinical treatment strategies for this condition are limited and often yield unsatisfactory outcomes. These approaches typically involve hormone replacement therapy combined with psychological support. Recently, mesenchymal stem cell (MSC) therapies for POI have garnered considerable attention in global research. MSCs can restore ovarian reproductive and endocrine functions through diverse mechanisms, including controlling differentiation, promoting angiogenesis, regulating ovarian fibrosis, inhibiting apoptosis, enhancing autocrine and paracrine effects, suppressing inflammation, modulating the immune system, and genetic regulation. This editorial offers a succinct summary of the application of MSC therapy in the context of POI, providing evidence for groundbreaking medical approaches that have potential to enhance reproductive health and overall well-being for women.

Key Words: Mesenchymal stem cell therapy; Mechanism; Premature ovarian insufficiency; Therapeutic; Women

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Core Tip: Premature ovarian insufficiency (POI) is an increasing cause of infertility globally, particularly among younger women, with profound effects on reproductive function and health. With limited treatment options and unsatisfactory results, the use of mesenchymal stem cell (MSC) therapies offers promising transformative approaches to restore ovarian function and enhance reproductive health in women. This article provides a concise overview and evidence of the potential benefits of MSC therapy for POI.

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INTRODUCTION

Premature ovarian insufficiency (POI), previously known as premature ovarian failure (POF), is associated with decreased ovarian function in women aged < 40 years, with its prevalence ranging from 1% to 4%[1]. POI not only affects fertility, psychological well-being, and overall quality of life, but it also significantly affects the skeletal, cardiovascular, urogenital, and nervous systems[2]. Its etiology involves a combination of genetic, immunological, environmental, and iatrogenic factors; however, the precise pathogenic mechanisms remain unclear. To date, there is no proven effective strategy that can restore ovarian function, and the current management approaches primarily encompass hormone replacement therapy, fertility management, and psychosocial support[3]. Although these therapies can partially alleviate clinical symptoms associated with POI, they cannot fully restore key aspects of ovarian function, such as hormone secretion, follicular development, and ovulation. In clinical practice, the most commonly employed method involves *in vitro* fertilization and embryo transfer, utilizing donated oocytes from young women[4]. Nonetheless, the application of this technique is limited by constraints related to the oocyte supply and ethical concerns, highlighting the evident need for new and effective treatments in the field of reproductive medicine.

In recent years, there have been significant advancements in the field of regenerative medicine, with stem cells and biomimetic materials emerging as prominent areas of research. Stem cells demonstrate pluripotent differentiation potential and the capacity for indefinite proliferation. These characteristics enable them to repair damaged tissues and enhance organ function, and therefore, they have significant prospects for treating various diseases, through transplantation[5-7]. Stem cells can be categorized based on their source, and they include embryonic and adult stem cells. Adult stem cells, obtained from undifferentiated cells in diverse tissues, such as bone marrow, adipose tissue, and placenta, have advantages that include their abundant availability, low immunogenicity, and ease of isolation and cultivation *in vitro*. Consequently, an increasing body of research suggests that mesenchymal stem cell (MSC) therapy can partially restore ovarian function and preserve fertility in patients affected by infertility[8-10], presenting a novel avenue for regenerative therapy with immense clinical potential. Therefore, advancing our comprehension of the underlying mechanisms of POI will facilitate further exploration in the field of reproductive medicine and guide the prudent application of MSCs for the treatment of infertility.

BONE MARROW MSCS

Bone marrow MSCs (BMSCs) are adult stem cells derived from bone marrow with noteworthy biological characteristics, such as pluripotent differentiation capacity across germ layers and multipotent differentiation potential. In recent years, several clinical studies have been conducted involving autologous BMSC transplantation based on more than 40 patients with POF. Remarkably, three patients successfully regained normal menstrual cycles, and two achieved pregnancy[11, 12]. Igboeli *et al*[13] documented two Caucasian patients with POF who exhibited restored ovarian hormone secretion, improved menstrual cycles, and alleviated menopausal symptoms after laparoscopic autologous BMSC transplantation into the ovaries. Clinical studies have also provided promising evidence for the utility of BMSC transplantation for patients with POF, to achieve successful pregnancies.

Notably, the role of BMSCs in restoring ovarian function has been validated using multiple animal models. The underlying mechanisms involve the suppression of inflammatory responses, inhibition of granulosa cell (GC) apoptosis, attenuation of ovarian tissue fibrosis, promotion of angiogenesis, and differentiation into GCs[14,15]. Early studies indicated that BMSCs are primarily located in the ovarian hilum and medulla, suggesting their potential involvement through paracrine actions[14,15]. Further investigations by Gabr *et al*[16] demonstrated that insulin-like growth factor-1 (IGF-1) and tumor necrosis factor- α induce BMSC homing *in vivo*. Moreover, Bao *et al*[17] and Park *et al*[18] reported that mice with POF who received BMSC treatment exhibit increased numbers of ovarian follicles at various stages, elevated sex hormone levels, and the restoration of ovarian reserves and fertility. Additionally, BMSCs significantly downregulate the mRNA expression of p21, BAX, and c-myc, thereby reducing GC apoptosis. Further, Fu *et al*[19] demonstrated that miR-21 overexpression in BMSCs enhances ovarian structure and function, which are impaired in a chemotherapy-induced POF rat model. This effect was found to be achieved through downregulation of the expression of phosphatase and tensin homolog and programmed cell death protein 4 genes, subsequently inhibiting GC apoptosis[19]. The latest

systematic review summarized the potential therapeutic mechanisms through which BMSCs can ameliorate POF. These mechanisms include homing, angiogenesis, anti-apoptosis, anti-inflammatory and immune regulation, paracrine signaling, mitochondrial transfer, autophagy, and anti-fibrosis and antioxidative effects[20].

ADIPOSE-DERIVED MSCS

Adipose tissue serves as a readily accessible source of stem cells with remarkable proliferative, differentiation, and immunoregulatory capacities. Accumulating evidence has demonstrated the anti-inflammatory, antioxidative, immunoregulatory, angiogenic, and regenerative properties of adipose-derived MSCs (ADMSCs). Studies have noted disturbances in the proportions of peripheral blood lymphocyte subsets in women with POF, including a decrease in the CD4+/CD8+ cell ratio[21]. ADMSCs can increase levels of transforming growth factor-beta1 and interleukin-10 in serum, resulting in expansion of the regulatory T cell population, thereby regulating immune functions and restoring ovarian function in POF[22]. Furthermore, ADMSC transplantation exerts an anti-apoptotic effect by modulating connexin 43 and pannexin 1 during the treatment of POI[23]. Co-culturing the extracellular vesicles of ADMSCs with GCs from women with POI has been found to promote cell proliferation, downregulate suppressor of mothers against decapentaplegic family protein expression, and inhibit the expression of genes associated with GC apoptosis[24]. Moreover, Ding *et al*[25] revealed that ADMSCs can activate the silent mating type information regulation 1 and forkhead box O1 (FOXO1) signaling pathway through the secretion of hepatocyte growth factor (HGF) and basic fibroblast growth factor (FGF), thereby alleviating oxidative stress injuries and restoring ovarian function in mice. In addition, Qu *et al*[26] demonstrated that ADMSC administration, through tail-vein injection, is a potential method to promote the restoration of chemotherapy-induced POF. This approach helps to attenuate apoptosis and senescence in ovarian GCs.

UMBILICAL CORD MSCS

Umbilical cord MSCs (UCMSCs) represent an additional promising source for stem cell transplantation therapy for POI. Clinical research conducted by Ding *et al*[27] demonstrated that UCMSCs activate primordial follicles by phosphorylating FOXO3 and FOXO1 proteins. Another clinical study reported successful births from four patients with POI after UCMSC transplantation, with a shorter duration of amenorrhea yielding more favorable outcomes[28]. The reparative effects of UCMSCs on the ovary have been observed using models of chemotherapy-induced injuries and natural aging[29]. Research has indicated that UCMSCs can restore the ovarian structure and function in mice with POI by regulating the Th1/Th2 cytokine ratio and the number of natural killer cells[30]. UCMSCs express heme oxygenase-1 and can improve ovarian functions in POI mice by modulating the autophagy pathway through activation of the c-Jun N-terminal kinase/B-cell lymphoma 2 signaling pathway and the circulation of CD8+CD28- T cells[31]. Furthermore, studies have evidenced that UCMSC transplantation results in the downregulation of superoxide dismutase and uncoupling protein 2 expression, suggesting potential mechanisms involving a reduction in oxidative stress and the mitigation of ovarian damage[32]. Additionally, Sun *et al*[33] reported that extracellular vesicles derived from UCMSCs inhibit chemotherapy drug-induced stress and apoptosis in ovarian GCs. These findings provide valuable insights for the future clinical application of UCMSCs for the treatment of POI. Moreover, Luo *et al*[34] discovered that therapy using human UCMSCs can restore ovarian functions in animals with POI by inhibiting the apoptosis of theca interstitial cells through the regulation of NR4A1-mediated mitochondrial mechanisms.

MENSTRUAL BLOOD-DERIVED MSCS

Menstrual blood-derived MSCs (MenSCs) offer several advantages, including their abundant sources, non-invasive acquisition, and low immunogenicity. As evidenced by a recent clinical trial involving 15 patients with POF, the intra-ovarian administration of MenSCs improved ovarian function and led to the restoration of menstrual cycles[35]. Research has also demonstrated that MenSCs can express multiple cell factors, such as HGF, IGF-1, and FGF-2, which promote GC maturation and differentiation *in vitro*. These cell factors play a significant role in ovarian repair[36]. Yamchi *et al*[37] reported that MenSC transplantation could modulate the expression levels of fibrosis-related genes, potentially restoring the structure and functions of damaged ovaries. Moreover, Fu *et al*[38] demonstrated that MenSC transplantation could improve the ovarian microenvironment by reducing GC apoptosis and ovarian stromal fibrosis. Further, Zhang *et al*[39] found that *in vivo*, the transplantation of extracellular vesicles derived from MenSCs promotes follicle development, restores estrous cycles and hormone levels, and improves pregnancy outcomes in rats with POI. Additionally, MenSCs were found to regulate the ovarian extracellular matrix composition, facilitate the recruitment of dormant follicles within the ovarian cortex, and enhance GC proliferation within follicles[39]. In conclusion, MenSCs present a promising and effective approach for the treatment of POI.

LIMITATIONS AND CHALLENGES ASSOCIATED WITH STEM CELL THERAPY FOR POI

Although the efficacy of stem cell transplantation has been extensively demonstrated based on numerous animal models, its clinical application remains relatively scarce. The methods and specifics of stem cell transplantation are still in the exploratory stage. Therefore, safety assessments for stem cell therapy remain a primary concern for infertility treatments for patients with POI. This is because when certain stem cells are transplanted into the body, they could lose their characteristic features, such as their high proliferation and differentiation capacity, and there is a chance of epigenetic modifications and chromosomal mutations, which can pose various risks. Moreover, their limited sources, associated ethical controversies, low survival rates of implanted cells, immune responses, and risks of tumor formation associated with stem cell transplantation add to these challenges. In recent years, research on the paracrine effects of stem cells has gained attention, and the concept of cell-free therapy for biologic treatments has emerged. Stem cell-derived extracellular vesicles, such as exosomes, have shown promise as a novel cell-free therapy for treating POI. For instance, Qu *et al*[26] reported that extracellular vesicles derived from human UCMSCs promote ovarian angiogenesis and inhibit ovarian GC apoptosis in a cisplatin-induced POF rat model through the delivery of miR-126-3p. Recently, a novel exosome-encapsulated microcarrier, prepared using microfluidic technology, was also presented for ovarian repair after chemotherapy-induced damage[40]. However, literature on cell-free therapy for infertility is currently limited, and further preclinical exploration is needed. Extensive experimental studies are crucial to explore the mechanisms underlying the effects of stem cell therapy for preserving female reproductive health. Large-scale clinical trials are also essential for ascertaining the safety and efficacy of stem cell therapy, with the goal of establishing a canonical consensus for future treatments.

CONCLUSION

We have provided a comprehensive overview of the application of different MSC types for the treatment of POI and have elucidated their potential mechanisms. The ultimate goal is to develop regenerative medicine and biomedical engineering strategies that can effectively cure POI. Although there are certain limitations to consider, a thorough understanding of the current research evidence is crucial for reproductive assistance agencies to formulate future translational applications and clinical trial guidelines for stem cell therapies for female infertility.

FOOTNOTES

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