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Stem cell-based therapeutic potential in female ovarian aging and infertility

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Abstract
Premature ovarian insufficiency (POI) is defined as onset of menopause characterized by amenorrhea, hypergonadotropism, and hypoestrogenism, before the age of 40 years. The POI is increasing, which seriously affects the quality of patients' life. Due to its diversity of pathogenic factors, complex pathogenesis and limited treatment methods, the search for finding effective treatment of POI has become a hotspot. Stem cells are characterized by the ability of self-renewal and differentiation and play an important role in the regeneration of injured tissues, which is therapy is expected to be used in the treatment of POI. The aim of this review is to summarize the pathogenic mechanisms and the research progress of POI treatment with stem cells from different sources.

Keywords Premature ovarian insufficiency, Ovarian aging, Stem cells, Fertility, Follicle, Exosome

Introduction

With the emergence of the aging society, aging problem has become a common social phenomenon, which has resulted in the occurrence and deterioration of many age-related diseases [1]. The female reproductive system has gradually become a vital health problem, because it is the first aging organ system of women [2, 3]. In particular, the aging of the female ovary is about decade prior to the natural function aging-associated functional decline of other general organs [4]. Influenced by many factors such as heredity, environment and behavior, ovarian aging finally manifests itself as menopause and affects multiple systems of the body, leading to the occurrence of related diseases [5, 6]. Ovarian aging not only includes age-related physiological aging, but also includes a variety of pathogenic factors leading to diminished ovarian dysfunction (DOR) and premature ovarian insufficiency (POI), which are special manifestations of ovarian aging at different stages or to different degrees [7, 8]. Age-related ovarian aging and is a natural and inevitable physiological aging process. In terms of pathological failure, this condition affects approximately 1% women, who suffer from hypoestrogenism and anovulation, and are characterized by primary or secondary amenorrhea, infertility, sex steroid deficiency and elevated gonadotropins [7]. Women with POI only have a 5–10% chance of conceiving at some time after diagnosis, the only proven means for infertility treatment being assisted conception with in vitro fertilization-embryo transfer (IVF-ET) and donated oocytes [9, 10]. However, the current routine clinical procedures of assisted reproductive technology (ART) cannot widely benefit all women undergoing IVF treatment with ovarian insufficiency. As a preventive strategy, cryopreservation of embryos/oocytes also has an economic burden, which is only applicable to a few high-income elderly women worldwide. So far, there

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is a lack of a successful treatment for age-related fertility decline.

Murase et al. [11] conducted a pivotal study that advanced our understanding of human germ cell epigenetic reprogramming in vitro. By differentiating human pluripotent stem cells into primordial germ cell-like cells (hPGCLCs) and expanding them significantly, they mimicked the early stages of human germ cell development. Their research highlighted the essential roles of BMP signaling and the MAPK (ERK) pathway in facilitating DNA demethylation and germ cell differentiation. Notably, the absence of TET1, a key DNA demethylase, redirected hPGCLCs towards becoming extra-embryonic cells and hindered the activation of crucial genes for gamete production. This study not only sheds light on the mechanisms of human germ cell development but also opens new possibilities for treating female ovarian aging and infertility through stem cell technology.Regardless of the safety issues that must be verified, somatic stem cells (SSCs) therapy has been the focus of considerable research in the field of reproductive medicine. Mesenchymal stem cell (MSC) therapy is considered to have great therapeutic promise for managing diminished ovarian function and has shown beneficial therapeutic effects in a variety of animal models of diminished ovarian function [12, 13]. MSCs are unique pluripotent stem cells with self-renewal ability, which also have capacity to differentiate into multiple cell lineages such as epithelial, stromal, and endothelial cells [14, 15]. These pluripotent cell masses were injected into the body through the tail vein, intraperitoneal and local transplantation, showing a huge recovery potential to improve ovarian function and save long-term infertility in the mammalian model of chemotherapy injury, which may participate in the process of cell proliferation and anti-apoptosis through paracrine effect [15, 16]. There are various sources of MSCs, such as adipose tissue, bone marrow, amniotic fluid, placental tissue, endometrium, menstrual blood, umbilical cord blood, urine, salivary gland and somatic cell reprogramming to regenerate individual specific pluripotent stem cells [17, 18]. Researchers have investigated their potential use as precursors of new follicle units, or whether they can be used to activate the remaining primordial follicles in the ovarian cortex to regain reproductive potential [19] However, previous studies also showed that the number of differentiated MSCs was not enough to explain the observed improvement in fertility, and there was still controversy about the issue of MSCs differentiating into oocytes after migrating to target tissues [9, 20, 21]. The present article provides a comprehensive review of the therapeutic potential of MSCs in premature ovarian insufficiency.

Search strategy and selection criteria

For this review, an extensive literature search was performed in Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, and Web of Science. Literature published in English and available up to December 2022 was included.

The following keywords were used for the search, alone or in combination: 'mesenchymal stem cells', 'diminished ovarian reserve', 'premature ovarian failure', 'premature ovarian insufficiency', 'ageing', 'ovarian ageing', 'infertility', 'transplantation', 'exosomes', 'extracellular vesicles', 'female reproductive diseases', 'follicles', 'intro fertilization treatment', 'embryo transfer'. Then, through the screening of titles and full-text of papers, only articles related to the topics of interest and related topics are selected for this review. In addition, we manually searched the references of relevant reviews and included ongoing researches to locate other potentially eligible materials.

Markers of prematre and physiological ovarian aging

Ovary may be the only organ that reaches its maximum potential before it is first used. Primordial follicles in female ovary have been completely formed before birth, known as 'ovarian reserve', which reflects the quantitative and qualitative of oocytes remaining in the ovaries [22, 23]. Follicle development needs to go through the stages of primordial follicle, primary follicle, preantral follicle, antral follicle to finally develop into mature follicle [24, 25]. At about 20 weeks of gestation, oogonia produced by mitotic division of primordial follicles are peak at 6 ~ 7 million [26]. However, the changes of development and external environment lead to the atresia and apoptosis of most follicles, which directly results in the decrease of the total number of follicles in the ovary. As a result, only 1 ~ 2 million follicles survive in the ovaries at birth and 300,000 ~ 500,000 by puberty [27]. During the reproductive period, the number of primordial follicles decreases at a steady rate of about 1000 per month. In fact, more than 99.9% of the primordial follicles undergo atresia at different stages of development, and only about 400 ~ 500 follicles will reach the ovulation stage in their lifetime [28, 29].

A remarkable feature of ovarian aging is accelerated consumption of primordial follicles and the reduction of antral follicles. Ovarian reserve is a major predictor of the age of natural menopause, and the unilateral increase of follicle stimulating hormone (FSH) is a recognized precursor of impending ovarian failure [30–32]. Although FSH has traditionally been used to predict ovarian reactivity during controlled ovarian hyperstimulation (COH) in infertile women, which levels are often elevated in women with clinical manifestations of decreased ovarian

reserve, serum FSH is not the best predictor of fertility decline, nor does it predict the timing of menopause [33].

Anti-Müllerian hormone (AMH) and inhibin-B have become biomarkers for evaluating ovarian reserve in infertile populations, which are both glycoproteins belong to the transforming growth factor beta superfamily and produced by granulosa cells in primordial follicle phase and initial phase of antral follicles [34, 35]. Therefore, the serum levels of AMH and inhibin-B are correlated with the number of antral follicles. Inhibin-B inhibits the increase of FSH in the early follicular stage [36]. AMH affects follicular genesis by altering the sensitivity of recruited primordial follicle, thereby maintaining the primordial follicle pool in a suspended state. Notably, serum inhibin-B and AMH levels decreased with age [37, 38]. Due to the fluctuation of serum FSH levels between different menstrual cycles, inhibin-B and AMH are better serological predictors of early ovarian reserve decline. However, low AMH levels do not necessarily result in decreased pregnancy rates in non-infertile populations.

Antral follicle count (AFC) is one of the most popular methods to explain ovarian functional status in clinical practice [25]. Ovarian aging is often accompanied by a decrease in the number of primordial follicles and early sinus follicles, and the changes of AFC and AMH between menstrual cycles are smaller than FSH or ovarian volume, so it is feasible to evaluate ovarian reserve by ultrasound guided AFC [25, 36, 39]. AFC and AMH are considered the best markers of ovarian response to stimulation in IVF cycles.

Mechanism of prematre ovarian insufficiency

Although the hormonal changes associated with ovarian aging are well characterized [40], the specific mechanisms leading to increased follicular depletion rate and granulosa cell apoptosis rate remain unclear. Ovarian aging involves multiple mechanisms and pathways, including genetic and metabolic, environmental and metabolic factors, mitochondrial dysfunction, oxidative stress, and the role of stem cells and telomerase (Fig. 1) [25, 41].

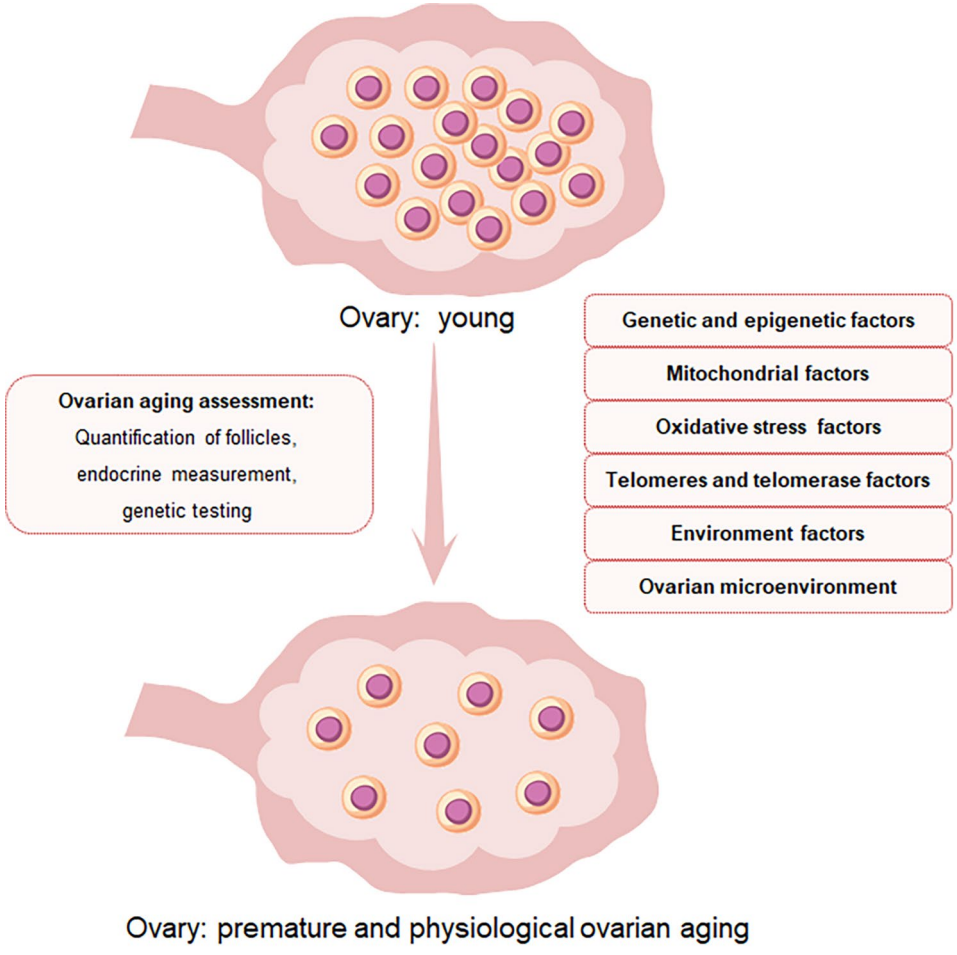

Fig. 1 Schematic representation of the number of follicles present in the ovaries and the quality of oocytes in relation to POI

Genetic factors

The abnormality of genetic factors is an important cause of POI, which can be derived from molecular heredity level as well as chromosome karyotype at cellular heredity level [42]. Follicle development requires the synergistic participation of many genes and signaling pathways. Any factors that lead to excessively small primordial follicle pool, disorders of follicle growth, recruitment or function, and acceleration of follicle depletion may lead to premature ovarian insufficiency and failure.

The disturbance of the migration and proliferation of primordial germ cells (PGC) can lead to the loss of ovarian germ cells and excessively small primordial follicle pool. The candidate genes involved in PGC forward migration and proliferation include POU class 5 homeobox (*POU5F1*) [43], Nanos homolog 3 (*NANOS3*) [44, 45], Autophagy-related gene 7 (*ATG7*) [46], *ATG9* [46], bone morphogenic protein 8B (*BMP8B*) [47], Diaphanous homolog 2 Drosophila (*DIAPH2*) [48] and meiosis related genes. After mitotic proliferation, PGC underwent the first meiosis and remained stationary in the prophase diploid phase, becoming the primary oocyte. During meiosis, mutations in key genes involved in DNA damage, mismatch repair, chromosome association and recombination can lead to meiosis failure, including MutS homolog 4 (MSH4), MSH5, DNA meiotic recombinase 1 (DMC1). Mice with deletion of the above genes showed varying degrees of infertility, and the ovarian eggs were depleted due to meiosis failure [49–51].

Primordia follicles are in a resting state after formation, which are either be activated, recruited, grown and ovulated or go to atresia and apoptosis. Primordial follicle activation is non-gonadotropin-dependent, and precise coordination between oocytes and somatic cells is essential at this stage. PTEN/PI3K/Akt/Cdkn1b signal and TSC/mTORC1 signal synergistic effect to maintain the balance between primorial follicle resting and activation [6]. Abnormalities of key signaling molecules can lead to over-activation of primorial follicle pool, accelerated follicle depletion, resulting POI and infertility [6].

Germ cell specific regulatory factors and transforming growth factors secreted by oocyte or granulosa cells are important regulatory factors involved in early follicle development. During follicle growth and development, different genes are normally expressed in sequence at different developmental stages, which requires fine regulation of ovaria-specific transcriptional regulatory network and cooperation between oocytes and granulosa cells. Recent studies have found that a variety of transcription factors specifically expressed in oocytes, such as folliculogenesis specific bHLH transcription factor (FIGLA) [52], newborn ovary homeobox gene (NOBOX) [53], LHX8 [43], spermatogenesis and oogenesis specific basic helix-loop-helix transcription factor 1 (SOHLH1) [54], SOHLH2 [55], form a complex and specific transcriptional regulatory network to regulate the specific gene expression in germ cells, thereby promoting early follicular development. Ovarian oocytes and granulosa cells can secrete a variety of transforming growth factors, such as bone morphogenetic proteins 15 (BMP15) [56], growth differentiation factor 9 (GDF9) [57], form a complex parasecretory network, mediate the connection between oocytes and surrounding somatic cells, promote the transition from primary follicle to secondary follicle, and regulate follicle development.

In the late stage of follicular development, growing follicles mature under the action of gonadotropin and sex hormone. Mutations of reproductive endocrine-related genes, such as *FSHR* [58], steroidogenic factor-1 (*SF-1*) [59], inhibin α (*INHA*) [60], estrogen receptor α (*ESR1*) [61], progesterone receptor membrane component 1 (*PGRMC1*) [62], can affect follicular recruitment, growth and function, and their pathogenicity in POI has long been paid attention to.

Mitochondrial function and mitochondrial dysfunction

Mitochondria are the most abundant organelles in oocytes and the energy source of oocytes [63]. They are characterized by their own genomes (mtDNA) and constitute the main maternal contribution to embryogenesis [63]. Mitochondria play an important role in the first developmental stage of the embryo prior to implantation, providing efficient and balanced energy consumption for the maturation of the ovum cytoplasm and nucleus, such as microtubule assembly and disassembly in the process of biofoaming rupture and meiosis spindle formation [64, 65].

Mitochondrial DNA levels were found to be reduced in POI patients [66, 67]. Reduced levels of mitochondrial DNA also occurred in older female mice compared with younger mice [68]. In contrast, elevated mitochondrial DNA levels in embryos were associated with reduced IVF implantation rates, reduced embryo survival, and increased risk of aneuploidy [69, 70]. The pathophysiological mechanism of these phenomena has not been fully elucidated, but it has been suggested that the increase of DNA copy number reflects the increase of stress level in oocyte and embryo [69, 70]. Studies [71, 72] have found that the level of reactive oxygen species in oocytes of older mice was significantly higher than that of younger mice after exposure to hydrogen peroxide, which also confirmed the rationality of the above theory. Mitochondria in primary follicular oocytes in older female mice tended to be smaller than in younger mice; however, this association was not found in other types of follicular oocytes [68].

Oocyte senescence is associated with mitochondrial dysfunction and decreased levels of oxidative

phosphorylation and ATP [73, 74]. This phenomenon may be mediated by SIRT1, an upstream regulator of mitochondrial genesis [75, 76]. Exposure to agents that cause mitochondrial dysfunction has been shown to increase SIRT1 expression in young cows [77]. It suggests that young oocytes may have better regulatory mechanisms and mitochondrial tolerance than older oocytes [67, 74]. Similarly, people who carry mutations in genes that cause mitochondrial dysfunction also develop POI [78, 79].

Oxidative stress

Reactive oxygen species (ROS) may cause cell senescence, and the increase of ROS level is associated with the decrease of oocyte maturation rate, fertilization rate, embryonic development and pregnancy rate [80–82]. Superoxide, hydrogen peroxide and hypo chloride can all enhance oocyte senescence with possible increasing the zona pellucida lysis time, changing the cytoplasmic microtubule dynamics of oocytes, and increasing the loss of cortical granules, especially in the oocytes of elderly patients [83].

With the aging of oocytes and granulosa cells, the expression level of antioxidant genes decreases, leading to DNA damage and cell apoptosis, which leads to the impairment of ovarian function [84]. By Raman spectroscopy, oocytes from young mice showed significant differences in fat and protein components compared with oocytes from ROS induced injury and old mice. Interestingly, young oocytes with ROs-induced damage showed similar levels of oxidative stress to older ovarian cells not exposed to exogenous ROS damage [85]. In the future, Raman spectroscopy may be a noninvasive way to evaluate oocyte oxidative damage and thus effectively predict oocyte quality [85].

Telomere

Telomeres are located at the ends of chromosomes of eukaryotes [86]. They are composed of multiple DNA duplicate sequences (TTAGGG) *n* and telomere-related proteins, which protect the ends of chromosomes and maintain the stability of genomes. The repetitive DNA sequence of telomeres is greatly shortened with each cell division. Telomere shortening can lead to chromosome terminal instability, DNA damage mutation and cell reconstitution defects. Therefore, telomere dysfunction has a very close relationship with aging or a variety of diseases [87]. Telomerase is an important factor in telomere length maintenance. Telomerase activity decreased with the increase of female age, which, in ovarian tissues, was significantly higher in women under 38 years old than in women over 38 years old. In conclusion, there is a potential relationship between ovarian follicle reserve and telomerase activity. In women with POI, telomere length and telomerase activity of follicular granulosa cells were lower than those in normal control group [88, 89]. In addition, sex hormones can activate telomerase activity and affect telomere length changes, which on the other hand also indicates the correlation between telomere and female reproductive aging [90, 91].

Environment factor

Exogenous factors affect ovarian follicle consumption rate and ovarian reserve function [92, 93]. Ovarian aging has been proved to be related to a variety of exogenous factors, such as smoking, radiation exposure, low socioeconomic status, extensive scar and chronic psychological stress caused by chemotherapy, pelvic surgery [93, 94]. These exogenous factors have ovarian toxicity. Some studies have found that air pollution can affect women's reproductive health [94]. In addition to increasing the risk of female infertility and abortion, it can also affect the reproductive system development of the next generation [95, 96]. A large-scale cross-sectional study found that exposure to air pollution during adolescence and early adulthood can lead to menstrual disorders in women, suggesting the correlation between air pollution and female reproductive tract diseases [97]. Environmental endocrine disruptors are widely used as preservatives, basic raw materials, insecticides, herbicides, spices and dye liquids for food, medicine and cosmetics [98]. A large amount of toxicological and epidemiological evidences show that exposure to environmental endocrine disruptors can cause harmful effects on women's health and is a potential risk factor for ovarian aging, which has attracted more and more attention from all sectors of society .

Ovarian microenvironment

Ovarian tissue consists of cortex and medulla, of which medulla is composed of connective tissue, fibrous tissue and blood vessels [99]. Ovarian microenvironment is composed of different types of cells in the ovary [99, 100]. The communication between eggs and microenvironment is mediated by direct contact with surrounding cells, extracellular matrix and signal molecules, including hormones, growth factors and metabolites [101]. Therefore, the ovarian microenvironment will affect the quality of eggs, and even accelerate the aging of eggs, leading to infertility and other diseases. Bidirectional communication between egg and its related somatic cells plays a key role in fertility and embryogenesis [102]. Cumulus cells can provide essential nutrients for oocyte maturation through different paracrine signaling pathways.

Changes in homeostasis between the synthesis and degradation of extracellular matrix (ECM) components affect tissue structure and function, while excessive accumulation of ECM can lead to tissue fibrosis. In addition

to heart, lung, kidney and other organs, there is also fibrosis in ovarian tissue [103]. The fibrosis in mouse ovarian matrix increases with the increase of reproductive age. Therefore, fibrosis is an early sign of ovarian matrix aging.

Mechanisms of STEM cells for treatment of POI

Stem cells are immortal or infinitely self-renewing cells that can produce genetically identical offspring or differentiate into a variety of specific tissue cells. In recent years, stem cells have been applied to the treatment of a variety of degenerative and injury-related diseases due to their multidirectional differentiation potential, providing a new direction for the clinical treatment of POI [104]. In previous studies, mesenchymal stem cells (MSCs), embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), and germline stem cells (GSCs) have been used for the treatment of ovarian dysfunction [105]. Compared with the current clinical treatment measures for POI, stem cell transplantation has the advantages of safety, non-toxic side effects, and can directly restore the ovarian function of patients, which is expected to fundamentally solve the problem of POI [106]. Therefore, it has become a research hotspot in the treatment of POI (Fig. 2).

Mesenchymal stem cells (MSCs)

Currently, MSCs are the most studied adult stem cells originating from mesoderm, which can be divided into bone marrow mesenchymal stem cells (BMSCs), umbilical cord mesenchymal stem cells (UMSCs), adipose stem cells (ADSCs), human amniotic mesenchymal stem cells (hAMSCs) and menstrual stem cells (MenSCs) according to tissue sources. BMSCs are adult stem cells with low immunogenicity, widely existing in the bone marrow microenvironment, which have the potential to self-renew and differentiate into a variety of tissue cells under certain conditions. In addition, BMSCs, easily isolated in vitro, can migrate to damaged ovaries to secrete key cytokines that improve ovarian function by anti-apoptosis, anti-fibrosis, anti-inflammatory, and immunomodulatory effects. Despite the low survival rate and limited differentiation potential of BMSCs after transplantation, some encouraging results have been achieved. Surprisingly, Prosper et al. found that autologous human mesenchymal stem cells increased estrogen production and reduced menopausal symptoms in women

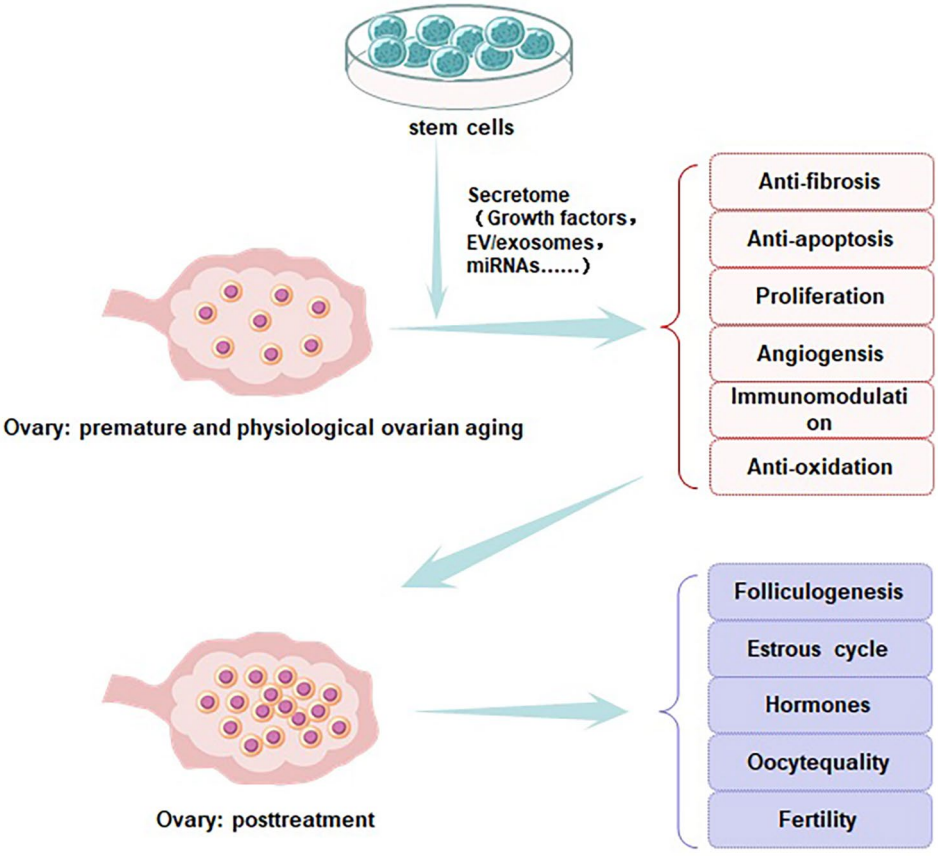

Fig. 2 Illustration of the stem cells improve ovarian function

with premature ovarian failure [107]. Chen et al. [108] reported a 38-year-old woman who was diagnosed with POI due to long-term use of hormonal drugs to treat polycystic ovary syndrome, after BMSCs treatment, the ovarian size returned to normal, endometrial thickened, and blood flow enhanced, suggesting that stem cell therapy for POI is a possible effective treatment strategy.

BMSCs can be enriched to the damaged ovary after intravenous injection to treat ovarian insufficiency. Chen et al. [109] showed that heat shock preconditioning enhanced the repair effect of BMSCs on chemotherapy-induced POI. The reason may be that the activity of BMSCs was further enhanced, which had a greater inhibition on apoptosis of granulosa cells. Gabr et al. [110] revealed that injected BMSCs could be implanted into the injured ovarian stroma, and the levels of insulin growth faction-I (IGF-I) and tumor necrosis faction-α (TNF-α) were increased, suggesting that they may play a role in the induction of BMSCs homing in vivo. Liu et al. [111] showed that after intravenous injection of BMSCs, BMSCs were mainly distributed in the portal and medulla of the ovary, a small amount of BMSCs were implanted in the ovarian cortex, but no BMSCs were observed in the follicles and corpus luteum, and the function and structure of the damaged ovary were eventually restored. It is worth noting that a study targeting the mare model found that the procedure of injecting allogeneic BMSCs into the ovaries is both simple and well-accepted [112]. However, under the conditions of this study, although BMSCs injection altered the gene expression in the ovaries, it did not have a significant impact on the evaluated ovarian function. These findings suggest that for age-related ovarian dysfunction, at least in the mare model, the use of BMSCs for intraovarian injection therapy is not supported, which may also be of relevance for women. This contrasts sharply with the established benefits of BMSCs in chemotherapy-induced damage in rat, mouse, and rabbit ovaries.

UMSCs have similar immunophenotype and functional characteristics to BMSCs, and both have multiplex differentiation potential and can secrete a variety of cytokines and growth factors. Currently, the clinical applications of UMSCs are focused on hematology and oncology. Studies have shown that UMSCs have the same potential for use in the treatment of non-hematopoietic diseases. Ding et al. [113] have demonstrated that UMSCs on a collagen scaffold can activate primordial follicles via phosphorylation of FOXO3a and FOXO1. Transplantation of UMSCs to the ovaries of POI patients rescued overall ovarian function, evidenced by elevated estradiol concentrations, improved follicular development, and increased number of antral follicles. Lu et al. [114] reported that after transplantation of UMSCs, serum estradiol, progesterone and interleukin-4 (IL-4) levels of mice with ovarian failure were increased, while serum FSH, interferon (IFN-γ) and IL-2 levels were decreased, and total number of healthy follicles was increased. The reduction of atretic follicles suggests that the recovery of ovarian function is regulated by cytokines secreted by Th1/Th2 cells after UMSCs transplantation.

Adipose tissue is a rich, low immunogenicity, stable proliferation, low damage and practical tissue source, which provides great hope for autologous cell repair and regeneration. ADSCs not only have the same biological characteristics as BMSCs, but also are easier to separate in large quantities than BMSCs. ADSCs can play therapeutic roles in the POI through paracrine and immune regulation mechanisms after transplantation, which has gradually attracted extensive attention of researchers. Sun et al. [115] reported that ADSCs could increase the number of follicles and oocytes in mice injected with cyclophosphamide by changing gene expression and paracrine cytokines. After ADSCs treatment, the expression of Zcchc11 was up-regulated and the apoptosis of granulosa cells was significantly reduced. This suggests that ADSCs treatment can significantly repair ovarian function after ovarian injury caused by chemotherapy.

Human amniotic membrane (hAM) consists of an outer layer of epithelial and connective tissue that is attached to the fetal skin above the umbilical cord and meets the sheep's water. hAM is composed of two different stem cell populations, human amniotic epithelial cells (hAECs) and hAMSCs. hAMSCs also have the ability of efficient multiple differentiation, which are easy to culture, obtain, and non-teratogenic. Due to hAM is usually discarded after delivery, and its use is restricted within legal and ethical frameworks, clinical research has been limited. Meanwhile, hAM-derived stem cells are less invasive than ADSCs and BMSCs. Studies have shown that hAECs and hAMSCs have good effects on POI mouse models. Yao et al. demonstrated that hAECs, could partly restore ovarian function, and the therapeutic function of intraperitoneally transplanted hAECs was mainly induced by paracrine-mediated ovarian protection and angiogenesis [116]. Ding et al. [72] reported that Exosomal miRNA-320a released from hAMSCs, can prevent reactive oxygen species generation in POI, through regulating Sirtuin4 (SIRT4) expression.

MenSCs exhibit MSc-like characteristics, including self-renewal, high proliferation rate, and the ability to multidifferentiate. Under certain conditions, Menscs can differentiate into various functional cells, including adipocytes, cardiomyocytes, bone cells, nerve cells, and endothelial cells. Compared to MSCs from other sources, MenSCs are easier to obtain and can be repeatedly sampled in a non-invasive manner. MenSCs have low immunogenicity and immunomodulatory function, which is one of the ideal cell types for tissue damage repair. Zhang

et al. [117] reported that concentrated exosomes from menstrual blood-derived stromal cells can improve ovarian activity in a rat model of premature ovarian insufficiency. Liu et al. [118] demonstrated that MenSCs can be stimulated to differentiate into ovarian tissue-like cells in the microenvironment of POI ovarian tissue, proving that MenSCs have the ability to restore POI ovarian damage.

Embryonic stem cells (ESCs) and Induced pluripotent stem cells (iPSCs)

In the process of allograft transplantation, BMSCs may have the risk of immune rejection, while in the process of autologous transplantation, BMSCs will also face the problems of insufficient sources caused by invasive surgery and tissue aging. There are no reproductive stem cells and new eggs occur in adult ovary. The eggs and follicles at birth are constantly exhausted with the growth of individual age, which inevitably leads to ovarian aging. If enough eggs can be obtained from outside the body and added to the ovaries in the body, it will be of great value to restore reproductive capacity and clinically treat ovarian aging related diseases, which is also a scientific problem that biologists around the world are competing to tackle. Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) are two common types of Pluripotent stem cells. The developmental potential of iPSCs is similar to that of ESCs, but iPSCs are superior to ESCs because of the avoidance of immune rejection and ethical issues. Zhang et al. [119] co-cultured rat ESCs and iPSCs with granulosa cells, and the results showed that the concentration of estradiol in the supernatant of the co-culture increased in a time-dependent manner, while that in the granulosa cell control group was on the contrary. Immunohistochemical staining confirmed that the expression of follicle stimulating hormone receptor increased in the co-culture group. These results suggest that rat iPSCs and ESCs can be effectively induced to differentiate into granulosa cells through indirect contact between cells. Liu et al. [120] used miR-17-3p to induce differentiation of human iPSCs into hormone-sensitive ovarian epithelioid cells in vitro, and then injected them into the POI model mice induced by cyclophosphamide. The results showed that the expressions of cytokeratin 7 and Erb proteins were up-regulated in the ovarian tissues of the hormone-sensitive ovarian epithelioid cell transplantation group. The expressions of fibronectin and vimentin were down-regulated, and ovarian weight and plasma estradiol levels increased over time in the transplant group. In another experiment, ovarian granulosa cells derived from human iPSCs were completely differentiated in vitro and transplanted into normal mice for stable growth, which could not only effectively promote the growth of granulosa cells and repair damaged ovarian tissue, but also maintain the ecological niche of ovarian tissue and promote the development and maturation of follicles in POI model mice [121].

Stem cell derived exosomes

Exosomes are vesicular bodies with a diameter of 40–100 nm secreted by cells, which carry proteins, mRNA and miRNAs to participate in intercellular communication. Exosomes are biologically stable with lipid bilayer membranes that prevent the degradation of inclusions and allow them to enter the target cells directly. This mode of signal transduction is efficient and stable, offering a novel and possible clinical cell-free therapy that avoids instability of cell origin and safety of allogenic cell infusion. Some studies have shown that exosomes secreted by stem cells can inhibit ovarian damage and alleviate age-related fertility decline in female mice. Yang et al. [122] suggested that BMScs-derived exosome miR-144-5p might promote follicle preservation after ovarian failure induced by chemotherapy through the PTEN/PI3K/AKT axis. This also suggested that exosome miRNAs are a key part of stem cell therapy for POI. Another study showed that placenta-derived mesenchymal stem cells reduce ROS levels by upregulating antioxidant enzymes in rat serum exosomes, thereby promoting cell proliferation and reducing cell apoptosis [123]. Tang et al. [124] demonstrated through their research that exosomes derived from UMSCs showed significant effects in alleviating cisplatin-induced cell damage by transferring anti-apoptotic miRNAs. These miRNAs within the exosomes targeted and regulated apoptosis-related pathways within the cells, thereby protecting granulosa cells from the toxic effects of chemotherapy drugs. Furthermore, Zhu et al. [125] further expanded our understanding of the role of stem cell-derived exosomes in protecting ovarian granulosa cells. They found that exosomal circBRCA1 stabilized by the m6A demethylase FTO could alleviate oxidative stress-induced cell damage, which was achieved through the miR-642a-5p/FOXO1 axis. The above studies collectively emphasize the importance and potential of stem cell-derived exosomes in protecting ovarian granulosa cells. By delving into the molecular components within these exosomes, such as specific miRNAs, we can not only gain a better understanding of how they regulate the survival and function of granulosa cells, but also lay the foundation for developing novel therapeutic strategies targeting women's reproductive health issues.

Stem cell derived mitochondria

In recent years, mitochondria derived from stem cells have shown great potential in improving POI. Mitochondria, as the energy factories of cells, play a crucial role in restoring ovarian function. Research by Liu et al. [126] has demonstrated that pyrroloquinoline quinone (PQQ) can promote mitochondrial function derived

from human mesenchymal stem cells (MSCs) by activating the SIRT1/ATM/p53 signaling pathway, thereby improving the condition of POI in mice. This finding not only reveals the potential role of PQQ in promoting mitochondrial function derived from MSCs but also provides a new mechanistic understanding for the treatment of POI. On the other hand, a study by Lu et al. [127] combines BMSCs with moxibustion therapy, pioneering the integration of traditional Chinese medicine with modern stem cell therapy for the treatment of POI. They found that this combination therapy can restore cyclophosphamide-induced POI by improving mitochondrial function and regulating mitochondrial autophagy. This research not only further confirms the important role of stem cell-derived mitochondria in restoring POI but also demonstrates the tremendous potential of combining traditional Chinese medicine with modern stem cell therapy. These studies emphasize the key role of stem cell-derived mitochondria in improving POI, whether through drug promotion or in combination with traditional therapies, opening up new pathways for the treatment of POI. With the continuous advancement of stem cell technology, especially in the application of improving mitochondrial function, we have reason to believe that there will be more treatment strategies for POI and other reproductive system diseases in the future, bringing new hope to patients. Additionally, these studies provide valuable knowledge to help us deepen our understanding of the pathological mechanisms of POI and develop more effective treatment methods.

Conlusions

The significant impact of POI on women should not be underestimated, and the research progress in utilizing stem cells from various tissue sources for treating POI is indeed a topic deserving attention. While basic experiments have shown promising results regarding the use of stem cells from different sources in treating POI patients, many underlying mechanisms remain unclear. Therefore, further expansion of experimental samples, along with clinical research and application, is necessary to validate the feasibility of such treatments. We propose fostering collaborations across disciplines such as biology, engineering, and computer science to leverage diverse expertise and accelerate the translation of experimental findings into practical applications.

The discovery of stem cells means that the treatment of POI patients will enter a new journey, which will make clinicians no longer limited to helping women complete the mission of maternity life, and it is more important to improve women's life quality, preserve fertility and delay aging. Looking ahead, while much work remains to be done, addressing the fundamental biological mechanisms behind stem cell biology will reveal new ways to optimize stem cell therapy.

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Author contributions
Xuan Jing chose the subject and gave guidance for every step. Xiangrong Cui searched the literature and wrote the article. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
This review study was based on published work and therefore did not require approved by an institutional committee.

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